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[1] Harrington, C. R.: "The Thyroid Gland," Oxford, 1933, p. 141.
[2] Meyer, A. E., and Wertz, A.: Endocrinology 24: 806, 1939.

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STUDIES CONCERNING THE CAUSE AND PURPOSE OF MENSTRUATION

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(*Presented before the Obstetrical Society of Boston on February 19, 1946.*)

MENSTRUATION, regarded as a normal process because of its practically universal occurrence among primates, still requires a complete answer as to its cause and purpose. Studies in this laboratory have been concerned with two components that appear to be involved in the menstrual phenomenon, the one toxic, the other hormonal. Because the reports on our findings have been somewhat scattered throughout the literature, a summary of them, as they particularly apply to menstruation, seems in order, together with our conclusions to date concerning toxic and hormonal interrelationships and a brief discussion of therapeutic implications.

THE TOXIC COMPONENT

Considerable evidence has accumulated indicating that menstruation is a toxic process (6). In 1923, Macht first presented scientific data showing the presence of a substance toxic to plants in the blood and other fluids of menstruating women (4). In his publications on the subject, however, only one reference is made to the study of the menstrual discharge itself (5). Our first experiments with this material, reported in 1940 (18), amply confirmed his observations as to its toxicity. From these and subsequent investigations (20, 22, 23), we conclude that the premenstrual regression

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of the endometrium which follows withdrawal of hormonal support involves the formation or liberation of a highly toxic protein which is eliminated in the menstrual discharge. This toxin, an atypical euglobulin, is most concentrated in the endometrial débris, is labile and lethal to rats and rabbits in very small doses. Its pathological effects are generalized tissue and pronounced vascular damage, as well as marked inflammatory reaction at the site of injection. Edema, hemorrhage and necrosis such as occur in the menstruating endometrium characterize the local and systemic reactions. Although not proven, it seems logical to assume that this toxin is the immediate cause of menstruation, the "bleeding factor." Abnormal absorption from the endometrium or inadequate bodily defense against it may well be responsible for the various subjective and objective phenomena related to menstruation. In support of this concept is the clinical observation that these phenomena are not manifest in the absence of the endometrium.

Menstrual discharge is markedly fibrinolytic (3, 22–24), as well as toxic, the enzymatic activity, according to our findings, being concentrated in the euglobulin fraction. We do not know whether the toxin and fibrinolysin are the same but are inclined to believe they are different entities, since fibrinolytic activity persists after toxicity has disappeared. Of promising therapeutic significance is the discovery that the pseudoglobulin fraction of the catamenial discharge is capable to a greater or less degree of protecting rats against an otherwise lethal dose of the toxin (23). Perhaps the toxin is an intermediary product of the action of the enzyme released by tissue injury. Possibly it, the enzyme and the protective pseudoglobulin are split-off components of endometrial cells during their catabolism resulting from hormone deprivation. Fibrinolytic activity, protection against the toxin, and evidence for the presence of toxin have been demonstrated also with the circulating blood of menstruating women but not with that taken between periods (23, 24). The work of Menkin on the pleural exudate of dogs following the injection of turpentine attracted our attention (20) because of the similarity between menstrual toxin and his more recently described "necrosin" (8). We now have evidence that they are identical, and, further, have found both fibrinolytic enzyme and protective pseudoglobulin in pleural exudates (22, 23). These findings invite the broad concept that cellular injury from causes other than hormone withdrawal and in sites other than the endometrium involves the formation or release of enzyme, toxin and protective factor. So far as menstruation is concerned, however, the primary cause of tissue catabolism must be hormone deprivation and the final precipitating factor resulting in débridement of the endometrium is logically the above-described, tissue-destroying, atypical euglobulin.

Since only the primates menstruate, must we conclude that this phenomenon is a mistake in the process of evolution? No satisfactory reason for this function has been established. We have postulated, however, for menstrual toxin a physiological rôle as a pituitary stimulant (13). There is experimental evidence for this. Early in our investigations we discovered that the toxic (euglobulin) fraction of menstrual discharge caused persistent functional corpora lutea in rats (19). Astwood had previously shown many damaging agents to have this effect through stimulation of the pituitary gland (1). Selye found enlargement of the adrenals to be a consistent reaction to "alarming" (noxious) stimuli and that this was mediated through the hypophysis (11). We have regularly observed adrenal enlargement in rats from menstrual toxin (18), and have recently demonstrated (by a technic previously described (16)) pituitary hypertrophy also with increased release of gonadotrophic as well as adrenotrophic hormones (15). Tepperman *et al.*, in reviewing the literature on adrenal hypertrophy have emphasized one point of similarity among the various conditions producing this effect, namely, protein catabolism, and have theorized that protein breakdown products stimulate adrenotrophic activity in the anterior hypophysis (28, 29). Our own data and Astwood's indicate that gonadotrophins are also released. Menstrual toxin, therefore, may well be an important factor in pituitary-ovarian and other interactions.[1] In further support of this idea is the repeated clinical observation of an earlier onset of the climacteric in patients who have undergone hysterectomy without removal of their ovaries. Since, however, ovulation does occur in animals and can occur in women without a preceding menstruation, the question may still be raised as to why the female primate should be subjected to a cyclic toxemia. One might think of menstruation as an evolutionary counterbalance to the greater bulk of cerebral cortex with its inhibiting and distorting influences on the vegetative systems both

[1] A rise in the gonadotrophic titer of urine has regularly been observed just before the start of menstruation (14, 30). There is indirect evidence also for increased adrenal cortical activity in relation to the onset of flow (10). The urinary excretion of antidiuretic substance at the time of menstruation has been reported (9) and suggests stimulation of posterior pituitary secretion. Premenstrual retention of water could be both an indirect effect of the toxin through posterior lobe activation and a direct effect on vascular permeability. Lyons, quoted by Freed (2), has demonstrated lactogenic hormone in the urine of menstruating women. Cyclic breast symptoms are minimal or absent when the endometrium is absent. Premenstrual soreness and engorgement of the breasts could be entirely an effect of lactogenic hormone on tissues prepared by the ovarian hormones. An added direct effect of toxin is conceivable. Moreover, since the epithelium of the breasts is a "target tissue" in the same sense that the endometrium is, it may be involved in a "menstrual" process of its own, this being asymptomatic unless sufficient lactogenic hormone and perhaps toxin are brought into play.

directly and through the hypophysis, as a supplement to hormonal interactions for keeping the hypophysis in a proper state of reactivity during the reproductive period of life.

THE HORMONAL COMPONENT

So far as the hormonal cause of endometrial bleeding is concerned, withdrawal of estrogenic stimulation is all that appears to be needed to result in tissue catabolism with its concomitant formation of toxin. Although, according to Markee (7), the observed processes in intraocular endometrial transplants are the same, there are, nevertheless, important differences between such anovulatory bleeding and that which follows withdrawal of progesterone or regression of a corpus luteum. Estrogenic bleeding is less predictable, both as to onset and duration; the disintegration of the endometrium is focal and prolonged rather than diffuse and more or less "explosive," as is the case in the normal postovulatory shedding. Furthermore, our studies (27) have revealed that progesterone-estrogen withdrawal differs from simple estrogen withdrawal in that it is characterized by a sudden, marked change in the urinary metabolites of estrogen, indicating increased oxidative inactivation. We have long felt that this change must be significant in the pituitary-ovarian interrelationship.

Animal experiments with Westerfeld's lactone, an oxidative inactivation product of crystalline estrone, have established the pituitary stimulating properties of this compound (16, 17) and strengthened our hypothesis that the physiological effects of estrogens vary depending upon their pathway of metabolism, oxidation products rather than the estrogens *per se* being responsible for stimulation of the pituitary with the release of adrenotrophic, gonadotrophic and perhaps other factors.[1]

Progesterone enhances the metabolic conversion of estradiol (the primary ovarian estrogen) to estrone and on to estriol, thus decreasing the oxidative inactivation that appears to take place in the reversible estradiol to estrone reaction (26). During the follicular phase of the cycle estradiol is secreted in increasing amounts as the follicle matures, and there is evidence that some progesterone is also secreted at this time (27) but always in insufficient amount to push the extradiol⇄estrone→estriol reaction predominantly to the right. The result is oxidative inactivation and release of pituitary gonadotrophins, *viz.*, luteinizing hormone (L.H.) and luteotrophin, these in turn first synergizing with follicle stimulating hormone (F.S.H.) to cause follicle maturation and ovulation, then causing luteinization, then maintaining the corpus luteum until sufficient progesterone is being secreted to convert estradiol and estrone on to the more stabile estriol (26). It is this effect of progesterone at the peak of luteal activity which, we believe, depresses oxidative inactivation, removes the source of pituitary-luteal stimulation and results in the subsequent regression of the corpus luteum. This regression allows follicular growth and estradiol secretion to begin again. In the absence of progesterone, during the premenstrual and early menstrual phase, conversion is minimal and oxidative inactivation marked.

The sudden increase in oxidation of estrogens at the start of postovulatory menstruation, therefore, supplies a "trigger-like" pituitary stimulus which is lacking in anovulatory flow and may well be essential for normal ovarian follicular development in the succeeding cycle.

The physiological importance of **progesterone**-estrogen withdrawal bleeding lies, we believe, in the more or less "explosive" stimulation of the hypophysis supplied both by the hormonal and toxic components at the time when F.S.H. has just been allowed to act on the ovaries through regression of the corpus luteum. Both the amount and timing of this stimulus depend upon withdrawal of progesterone. Unless menstruation is preceded by the inhibiting influence of progesterone upon follicular development, this may have gone beyond the stage of optimum responsiveness to the gonadotrophic stimuli released by toxin and oxidized estrogens. In anovulatory flow the focal breakdown of the endometrium indicates to us that toxin formation also may be focal, sporadic and inadequate both for diffuse shedding and sufficient pituitary stimulation. (We have evidence (15) that the discharge in anovulatory menstruation contains less toxin.) No sudden, marked increase in oxidative inactivation products of the estrogens is found at the start of the anovulatory bleeding where the process is merely the result of fluctuations in the level of the estrogens without the controlling influence of the corpus luteum. Objective evidence of the physiological importance of progesterone-estrogen withdrawal bleeding was supplied by a study of urinary metabolites of estrogen in a woman with typical dysfunctional flowing during cyclic estrogen-progesterone therapy (26). The results indicated progressively more normal ovarian activity during a series of treatments and, finally, ovulation and luteinization. Spontaneous periods from a secretory endometrium ensued at monthly intervals.

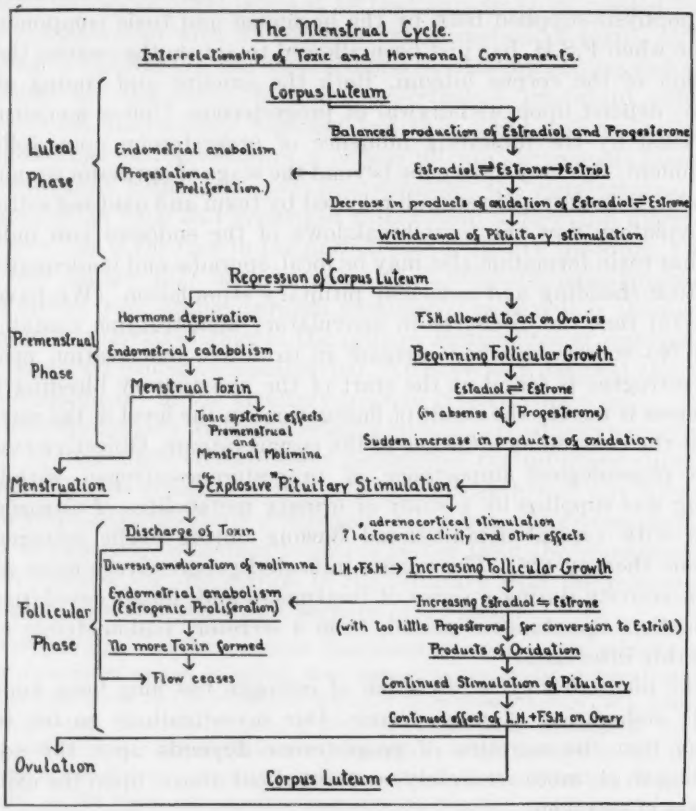
In the menstrual cycle, secretion of estrogen has long been known to precede elaboration of progesterone. Our investigations go far toward showing that the secretion of progesterone **depends** upon the estrogen preceding it, or, more accurately, as pointed out above, upon the oxidation products of estrogen.

The accompanying chart summarizes our conception of the processes involved in the normal cycle.

THERAPEUTIC IMPLICATIONS

Specific suggestions for the hormonal treatment of functional gynecological disorders, based on the above information and experience, have been published (12, 25). In any attempt to correct menstrual abnormalities, *viz.*, amenorrhea, skipped or delayed periods, too frequent periods and dysfunctional flowing (menorrhagia and metrorrhagia), we recom-

mend the cyclic artificial production of a hormonal situation which will result in a postovulatory-like menstruation, *i.e.*, a mimicking of the normal cycle as closely as possible. One should aim at using enough progesterone and not too much estrogen. Available information indicates that the mature corpus luteum secretes at least 50 mg. of progesterone a



day (26) and that the ovarian secretion of estrogen, presumably estradiol, varies from about 0.08 mg. to about 0.70 mg. daily, with a daily average of 0.30±mg. (27). Commercial production being what it is, one cannot give too much progesterone these days, but may and often does administer too much estrogen to the non-pregnant woman, the result being inhibition of F.S.H. and loss of that effect on the ovaries when it is needed.

One might question the giving of estrogen at all to those cases in whom there is evidence of estrogenic activity, *e.g.*, the patient with dysfunctional

flowing associated with follicular cysts and endometrial hyperplasia. According to our studies (26), estrogen as well as progesterone is deficient in such a case, the endometrial effect being presumably the result of prolonged exposure to subnormal amounts. In fact, we have yet to find a situation associated with progesterone deficiency in which estrogens are not also below par. This is reasonable if one accepts the concept that secretion of progesterone depends upon estrogen and remembers that the well-developed corpus luteum secretes more estrogen than does the follicle at any stage of development.

In certain disorders, *e.g.*, functional menorrhagia from a secretory endometrium and premenstrual tension or distress, we have reasoned that the corpus luteum is below normal in its hormone production, so that its regression is prolonged with a resultant "teetering" of the premenstrual hormonal and endometrial changes. Premenstrual molimina may well reflect abnormal absorption of toxin as a consequence of this situation. Theoretically, all that is needed is a better corpus luteum. Estrogen alone, given throughout the cycle except during flow, has often relieved such cases, presumably through the stimulation of pituitary L.H. and luteotrophin. In the intact rat we have found diethylstilbestrol 100 times as active as estrone as a pituitary stimulant (21). This is the experimental basis of our preference for this drug in practice, a preference borne out by results so long as the daily dose does not exceed 0.3 mg.

When, however, the disability is definitely associated with failure to ovulate and form a corpus luteum, any treatment should be aimed towards initiating ovulation and, in our experience, this is most often accomplished by cyclic administration of estrogen and progesterone (*i.e.*, 0.3 mg. or less of stilbestrol daily by mouth through the 20th to 25th day, plus 10 to 25 mg. of progesterone daily by injection for 5 days beginning on the 21st day). The number of cycles of therapy that should be tried before considering the treatment a failure differs. Our most gratifying results have been in cases of typical dysfunctional flowing where two to four cycles are often sufficient to reestablish a normal pituitary-ovarian interrelationship. In functional amenorrhea larger doses of estrogen should be given for a time, for "priming" purposes, before starting progesterone administration. A few successes may be achieved, but only after many months of the cyclic production of estrogen and progesterone withdrawal bleeding.[2]

[2] Since "functional" amenorrhea may be due to some basic congenital or acquired defect, it would seem desirable to employ gonadotrophic extracts as substitutional therapy in these cases. Such extracts, however, are not yet dependable and may be harmful, due to reactions and antibody formation.

If, as we are led to suspect, premenstrual disorders (*e.g.*, tension, headache, distress, sore breasts (?), etc.) and menstrual molimina (primary dysmenorrhea, nausea and vomiting, convulsions, disorientation, exacerbation of epilepsy, etc.) are caused by excessive absorption of or abnormal sensitivity to menstrual toxin, some means of neutralization should be beneficial. The protective pseudoglobulin found in association with the toxin (23) offers therapeutic possibilities and we are now attempting to purify and concentrate this factor from the pseudoglobulin fractions of the venous plasma of menstruating women and of human pleural exudates.

SUMMARY

Menstrual toxin, a euglobulin-like material in the menstrual discharge whose pathological effect is one of generalized vascular damage, may be logically supposed to be the "bleeding factor," the precipitating cause of flow. Its formation or release appears to depend solely upon the endometrial catabolism which results from hormone deprivation. The indication that "noxious" stimuli cause the release of pituitary gonadotrophic as well as adrenotrophic factors suggests for the menstrual toxin a physiological rôle in the regulation of ovarian activity.

The finding that progesterone inhibits the oxidative inactivation of estrogens, and that oxidative inactivation products rather than estrogens *per se* are responsible for the release of pituitary gonadotropes, considerably clarifies our understanding of the cyclic nature of ovarian activity. Although estrogen withdrawal is all that is needed for endometrial catabolism with the consequent release of toxin and flow, luteinization of the ovarian follicle has, nevertheless, a regulatory influence both upon endometrial and hormonal changes during the premenstrual phase which is lacking in anovulatory cycles. Regression of the corpus luteum or the artificial production of estrogen-**progesterone** withdrawal bleeding is characteristically accompanied by a diffuse release of toxin throughout the endometrium, as evidenced by the type of flow, and by a sudden, marked increase in oxidative inactivation products of the estrogens. These two components appear to combine to supply a trigger-like release of pituitary gonadotrophic factors which is lacking in estrogenic bleeding and which may well be important for complete development of the ovarian follicle during the succeeding cycle.

Hormonal treatment of functional gynecological disorders based upon these findings is briefly discussed. The discovery that the pseudoglobulin fraction of menstrual discharge, of the plasma of menstruating women, and of human pleural exudates contains a factor capable of protecting rats against an otherwise lethal dose of menstrual toxin offers therapeutic possibilities for the treatment of various premenstrual and menstrual

disabilities which may result from excessive absorption of menstrual toxin or inadequate bodily defenses against it.

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CHRONIC IDIOPATHIC HYPOPARATHYROIDISM WITH SUPERIMPOSED ADDISON'S DISEASE IN A CHILD

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CASE reports of hypoparathyroidism following thyroidectomy far outnumber those of idiopathic parathyroid deficiency. As late as 1939 Drake *et al.* (10) found only eight established cases in the literature (2, 3, 5, 6, 21, 26, 27), to which they added six cases of their own. To date 20 more cases have been reported (4, 7, 12, 13, 15, 19, 23, 24, 34, 39, 40, 41, 44). Of these 34 cases, 24 had their onset of symptoms before the age of 15, and only two, both children, showed associated signs of adrenal insufficiency. The rare occurrence of combined parathyroid and adrenal insufficiency, and the absence of previous pathological reports in such cases in the modern literature prompted the following case report.

CASE REPORT[1]

First admission: *E. K.* was admitted to the New York Nursery and Child's Hospital in June, 1934, at the age of 9½ years because of convulsions. Her birth and early development had been normal. Convulsive seizures began at three years of age and recurred at approximately yearly intervals. At the age of five years her serum calcium was found to be 5 mg. percent, and a diagnosis of tetany was made. In the interval between January and June, 1934, she had three convulsions, each preceded by frontal headache and vomiting of two to three weeks' duration.

Examination on admission revealed alopecia, carpopedal spasm, and a positive Chvostek sign. The values of the daily determinations of serum and urine calcium and inorganic phosphate, and the effect of parathormone by intramuscular injection are shown graphically in Figure 1.

Following therapy all evidence of tetany disappeared. The patient was discharged in July, 1934, on a high calcium diet with daily supplements of calcium gluconate. In the succeeding nine months she had no symptoms except occasional vomiting, headache, and pain in extremities. Progressively falling levels of serum calcium were transiently reversed by intramuscular injections of 200 units (2 cc.) of parathormone at two to three month intervals.

Second admission: She was readmitted to the New York Hospital on April 16, 1935, with a history of a respiratory infection for two weeks, pains in the extremities for one day, and a severe generalized convulsion on the night of admission. She was obese with moderate accentuation of fat distribution about the breasts, waist, and hips. Her hair was thin, fine and silky, with patches of baldness. The teeth were widely separated, with

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[1] Permission granted by Dr. Arthur Anderson for reporting this case.

hypoplastic bicuspids not covered by enamel. The skin was darkly pigmented, and pubic hair was absent. The pharynx was acutely inflamed, and both ear drums were injected. Pretibial edema was present. Vision was good, and there were no lenticular opacities, but bilateral papilledema of from three to four diopters, with numerous large hemorrhages, was noted. Chvostek's sign was equivocal; Trousseau's sign was positive. Blood pressure was 110/80 mm. Hg. Psychometric study showed an I.Q. of 80 percent. The hemoglobin was 13 grams; the erythrocyte count, 4,520,000 per cu. mm.; leucocyte count, 28,300 per cu. mm., with 60 percent adult polymorphonuclear leucocytes, 15 percent immature polymorphs, 20 percent lymphocytes, 3 percent monocytes, 1 percent each of eosinophiles

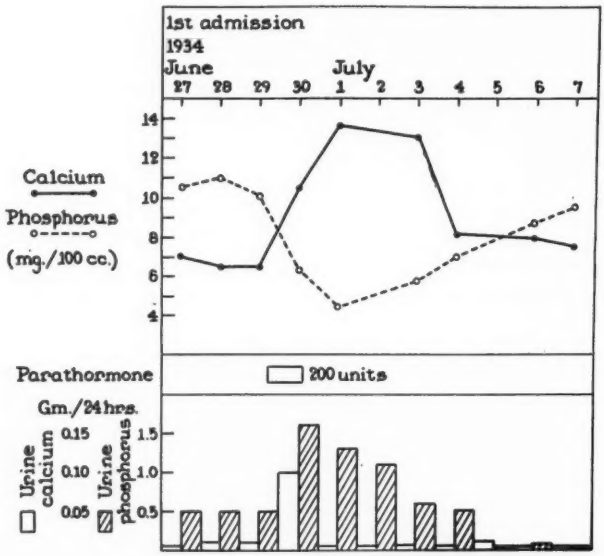

FIG. 1. Response of calcium and phosphorus levels in blood and urine following a single large injection of parathormone.

and basophiles. The urine initially showed a trace of albumin and acetone, many leucocytes, a few erythrocytes, and no casts, but numerous subsequent examinations throughout the remainder of her illness were normal. The Kline test was negative. A lumbar puncture produced clear spinal fluid under a pressure of 180 mm. of water; the fluid contained four leucocytes per cu. mm. and there was a normal value for protein, chlorides, and sugar. The Wassermann reaction of the spinal fluid was negative. An intradermal test with 0.1 mg. of old tuberculin was negative. The serum calcium was 7.0 mg. percent, phosphorus, 6.4 mg. per cent. Roentgenograms of the skull showed a large cranial vault with prominent vascular channels, a normal sella turcica, and several vague shadows of intracranial calcification. The long bones showed slight generalized decalcification.

The patient was placed on a regimen of oral calcium lactate and intermittent intramuscular injections of parathormone. The effect of this therapy on serum calcium and phosphorus and urinary calcium is shown in Figure 2. The respiratory infection subsided,

and peripheral edema disappeared. The Chvostek and Trousseau reactions became negative. From May 11th to June 29th balance studies were carried out while the patient was on a constant diet, with a daily calcium intake of from 0.872 gm. to 1.161 gm. (calculated from Sherman's tables, supplemented by a few analyses) and a phosphorus intake of from 0.979 gm. to 1.389 gm. Quantitative analyses of urine for calcium, phos-

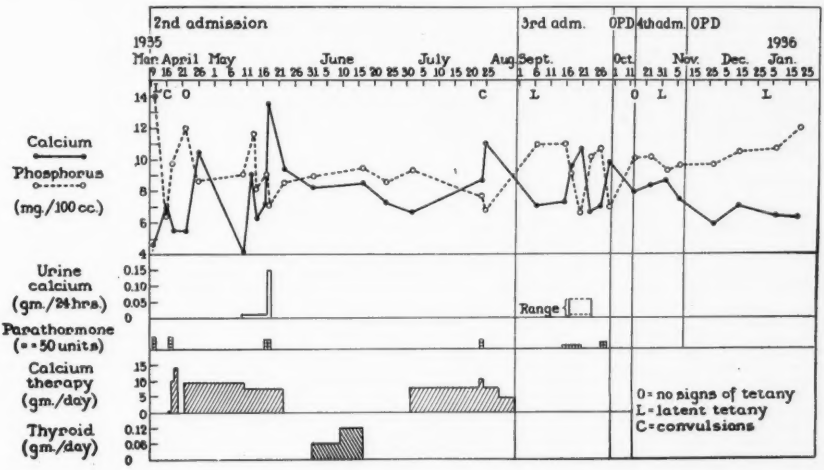

FIG. 2. Fluctuations of serum calcium and phosphorus and urine calcium in response to calcium lactate, parathormone, and thyroid therapy.

phorus, creatin, and creatinin, and stool analyses for calcium and phorphorus were performed for 15 consecutive, three or four day periods with no therapy, with calcium lactate, and with desiccated thyroid. The addition of calcium lactate caused a marked positive increase in calcium and phosphorus balances (Table 1). With thyroid therapy there was no significant change in the phosphorus balance, but the calcium balance became slightly negative. The urine creatinin fluctuated mainly between 0.444 gm. and 0.590 gm. per 24 hours with extreme values of 0.249 gm. and 0.758 gm. Creatinuria ap-

TABLE 1. CALCIUM AND PHOSPHORUS BALANCE DETERMINATIONS

	No. of days	Calcium (av., grams/24 hr.)				Phosphorus (av., grams/24 hr.)				Therapy
		Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance	
First Admission	9	1.930	0.016	1.467	+0.447	1.168	0.098	0.605	+0.465	Calcium lactate, 7.2 gm.
	6	0.955	0.031	0.853	+0.071	1.105	0.416	0.559	+0.130	None
	9	1.006	0.027	1.001	−0.022	1.279	0.469	0.634	+0.176	Thyroid, 0.06 gm.
	7	1.043	0.033	1.011	−0.001	1.293	0.435	0.674	+0.184	Thyroid, 0.12 gm.
	12	1.065	0.005	0.907	+0.153	1.312	0.258	0.710	+0.344	None
Third Admission	7	1.035	0.006	0.905	+0.124	1.169	0.322	0.721	+0.126	None
	6	0.956	0.024	0.633	+0.299	1.125	0.595	0.474	+0.056	Parathormone, 50 u
	6	1.051	0.016	1.152	−0.117	1.158	0.267	0.841	+0.050	None

TABLE 2. BLOOD CHEMISTRY DETERMINATIONS

Adm.	Date	CO_2 Content vol. %	Urea N mg. %	NPN mg. %	Serum protein gm. %	Serum albumin gm. %	Cholesterol mg. %	Sugar mg. %	Phosphatase units	Sodium m. eq./l	Chlorides m. eq./l	Potassium m. eq./l	BMR
2	4-16-35	52											
	4-17-35		12		6.8	3.5	112						
	4-26-35	61.1			7.9					126.2	86.4		
	5-10-35									136.5	97.6		
	5-13-35				7.0	4.1							
	5-18-35									143.8			
	5-20-35								3.7				
	6- 4-35												−10
	6-10-35												+ 3.1
	6-17-35												+ 2.5
	6-24-35									142.2			
	7- 2-35									137.3			
4	11- 9-35								5.5				
5	2-14-36									133.4	92.5		
6	4-14-36		14					62					
	4-22-36						161			Fig. 3			−10
	4-24-36							89.6					
	5- 8-36			35.4									
7	5-15-36			26.2									
	5-26-36			37.6									
	7-15-36									Fig. 3		3.49	
	8- 4-36				7.0							3.92	
	8-19-36				6.24							3.91	
8	11-19-36											4.12	
	12- 1-36									Fig. 3			−10
	12- 2-36						168	56					
	12- 3-36							121					

peared only during and for 3 days after thyroid administration (0.024 gm. to 0.379 gm. per 24 hours). On July 24th the patient had her only convulsion during this admission. Parathormone therapy and intravenous calcium gluconate afforded prompt clinical relief and laboratory improvement (Figure 2). Blood chemistry values other than calcium and phosphorus are recorded in Table 2.

Third admission: On readmission on September 6, 1935, the papilledema had decreased, leaving only a slight fuzziness of the disks. The serum calcium and phosphorus values and the response to therapy are recorded in Figure 2. From September 9th to September 28th calcium, phosphorus, and nitrogen balance studies were performed with periods of seven days with no therapy, six days while receiving 50 units of parathormone daily, and six days again without therapy. There was a significant increase in positive calcium balance during the administration of parathormone, followed by a negative balance when this treatment was stopped. Phosphorus retention was decreased both during and after parathormone therapy (Table 1). The patient was in negative nitrogen balance during this entire period.

Fourth admission: Readmission for parathyroid transplantation was advised on October 14, 1935. Because she was asymptomatic and showed slight spontaneous improvement in her laboratory findings during her stay of almost four weeks (Figure 2), surgery was deferred. Prior to discharge on November 9, studies of muscle response to galvanic stimulation gave the following readings: cathode closing, 1.5; anode closing, 1.5; anode opening, 4.0; and cathode opening, 5.0.

Fifth admission: During the next three months at home the patient developed photophobia and impairment of vision, diagnosed as phlyctenular conjunctivitis, and this responded temporarily to local therapy. She was readmitted on February 3, 1936, for pains in the extremities. She had marked blepharospasm secondary to almost healed corneal ulcers. Chvostek's sign was markedly positive. At discharge on February 14th, the skin was noted to be darker than on admission, and the blood pressure had fallen from 110/80 mm. Hg. to 85/65 mm. Hg.

Sixth admission: During the next two months her condition rapidly deteriorated. The skin pigmentation deepened, photophobia increased, and anorexia resulted in a loss of 5.9 kg. (13 pounds). She was readmitted on April 6, 1936, because of pains in the arms and legs, headache, and vomiting. She was now poorly nourished and chronically ill. The skin was dry, brown-black, with accentuation of pigmentation in the folds and on the gingival surfaces. Marked photophobia prevented visualization of the fundi, and several corneal scars and ulcers were present. Chvostek's sign was negative. The blood pressure was 86/46 mm. Hg. Despite parathormone therapy the pains in the extremities and vomiting persisted. On April 8th after repeated vomiting, she went into shock with a blood pressure of 40/0 mm. Hg. It was now evident that the manifestations of adrenal insufficiency, which had been increasing slowly for a year, had culminated in an adrenal crisis, and this clinical impression was confirmed by the serum sodium value of 125 m.eq./liter. Crude adrenal cortical extract (*Eschatin*) and dextrose and saline were given parenterally, followed by maintenance oral doses of sodium chloride. Improvement was rapid, the blood pressure rising to 100/50 mm. Hg. and remaining within the normal range for the duration of this admission. Vomiting ceased, and photophobia diminished. Convulsions on May 2nd and May 8th led to resumption of parathormone treatment for six days and a diet containing high sodium, high calcium, low phosphorus, and low potassium (Figure 3). During this period the hemoglobin fell gradually from 13.2 gm. to 8.4 gm. without apparent cause. She was discharged on May 15th to continue the same diet at home, with the addition of iron and ammonium citrate and sodium chloride.

Seventh admission: Another convulsion required readmission three days later, when the physical examination was unchanged except for a positive Chvostek's sign. Blood pressure was 110/70 mm. Hg. The same dietary regimen with injections of parathormone controlled the convulsive seizures, and after the addition of 30 gm. of calcium lactate to the daily diet no further convulsions occurred. Serum calcium and phosphorus values were better maintained than at any previous time (Figure 3). On June 9th ventriculo-

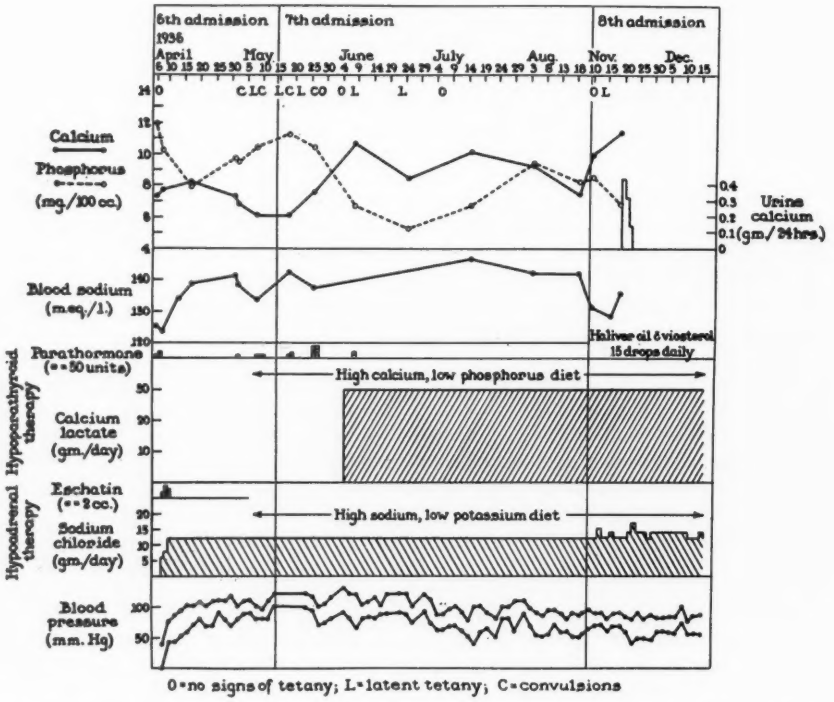

FIG. 3. Fluctuations of tetanic symptoms, blood pressure, and serum calcium, phosphorus, and sodium, correlated with therapy of parathyroid and adrenal insufficiencies.

grams revealed only slight dilatation of the third ventricle. Irregular intracranial deposits of calcium were seen in both hemispheres. For the next two months the patient was free of symptoms of tetany, and at the time of discharge on August 22nd, serum calcium was 7.37 mg. percent, phosphorus, 8.08 mg. percent, and sodium, 141.9 m. eq. per liter.

Eighth admission: The last admission occurred on November 9, 1936, with the complaints of diminished appetite, pain in legs, pain in eyes, impairment of vision, and drowsiness for a month. She was a deeply pigmented, poorly nourished girl, mentally retarded, with very sparse hair and brittle splitting nails. Marked deepening of the pigmentation is seen in the photograph, in comparison with one taken six months previously (Figure 4). Chvostek's and Trousseau's signs were negative. The blood pressure

was 96/64 mm. Hg. Her height was 134 cm. and weight, 26.5 kg. Therapy consisted of haliver oil and viosterol 15 drops daily in addition to the diet, sodium chloride, calcium lactate, and iron. The patient remained irritable and disinterested, lying much of the time with her head buried in a pillow. Her blood pressure remained low—systolic pressure 60–90 mm. Hg., diastolic, 25–70 mm. Hg. She vomited daily, and complained frequently of severe abdominal pain, unaccompanied by tenderness and relieved by intrevenous saline. Roentgenogram of the skull on December 4th showed a marked increase of the large areas of mottled calcium about two centimeters above and posterior to the

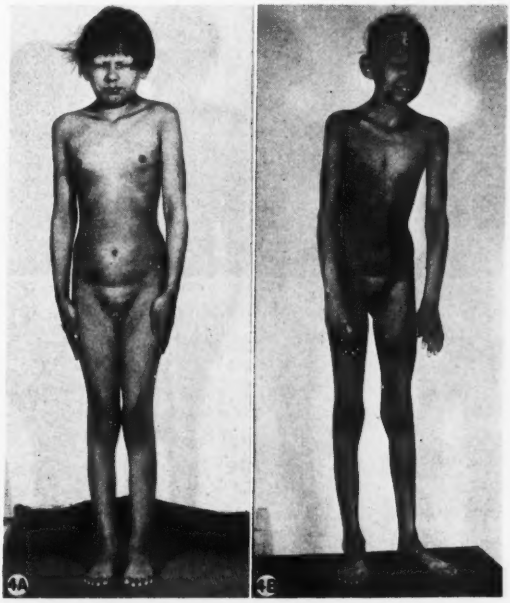

FIG. 4. (a) Photograph on May 4, 1936. (b) Photograph on November 27, 1936, showing increased pigmentation, malnutrition, and alopecia.

sella on both sides of the midline (Figure 5). A gastro-intestinal series and barium enema were negative. At about 8 p.m. on December 17th the patient complained of severe paroxysmal pains in her abdomen and legs, and said she was going to die. Within 10 minutes she became pulseless, unconscious, and died, in spite of the administration of adrenaline, caffeine, and crude adrenal cortical extract.

POST-MORTEM EXAMINATION[2]

Gross findings: The skin was diffusely pigmented, and scalp hair was practically absent. All lobes of the lungs were increased in consistency, but without distinct areas of

[2] Autopsy was performed by Dr. Robert Moore, and the sections were reviewed by Dr. C. M. Flory.

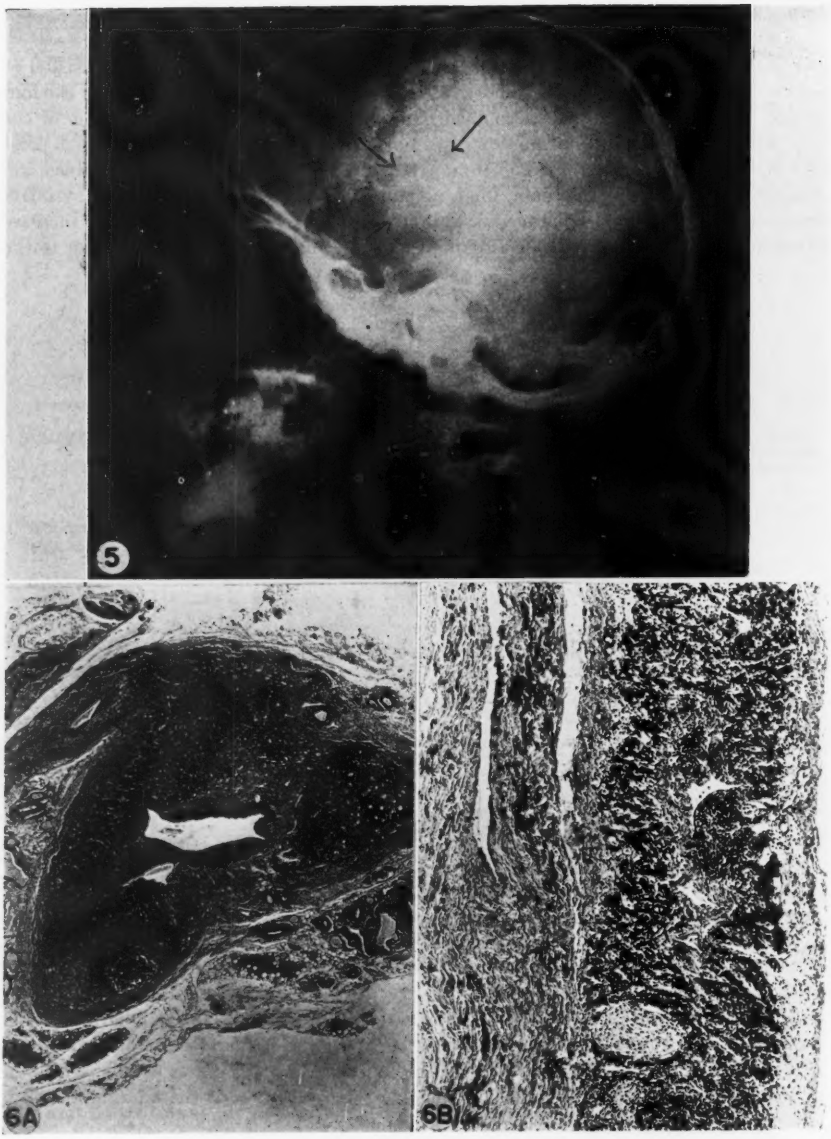

FIG. 5. Roentgenogram of skull, showing diffuse intracranial calcification.

FIG. 6. (a) Cross section of entire adrenal gland. No cortical tissue remains. A small amount of medullary tissue can be seen about the central vein. Surrounding this are large masses of lymphocytes and some connective tissue (hematoxylin and eosin stain, ×30).

(b) Cross section of other adrenal, showing, a few small clusters of lymphocytes in and around medulla. No cortex remains. (Hematoxylin and eosin stain, ×90).

consolidation. A large quantity of blood-tinged frothy fluid exuded from their cut surfaces. The lymphoid tissue at the base of the tongue and tonsils was moderately enlarged; that of the small and large intestine was conspicuously enlarged. Mediastinal, cervical, axillary, and mesenteric lymph nodes were of moderate size with distinct cortices and congested medullary portions. Brain, heart, liver, spleen, kidneys, and bone marrow were grossly normal.

Careful dissection of the neck failed to reveal any parathyroid glands. Several small masses taken for section proved to be lymph nodes. The adrenals weighed only one gram each [normal for an 11 to 15 year old girl, 7.99 gm. each (30)], did not exceed 2 mm. in thickness, and showed no definite architecture on section. The thymus weighed 21 gm., with the usual glandular lobulated structure. The thyroid gland weighed 8.6 gm., and contained a moderate amount of colloid. The pancreas was normal. No grossly identifiable follicles were seen in the ovaries. The uterus and tubes were very small. The pituitary gland measured 7.5 mm. by 12.5 mm. by 4.5 mm., weighed 280 mg. [normal 500 mg. (30)], and had a normal structure grossly.

Histological examination: The alveoli of the lungs contained scattered granular acidophilic debris without cellular exudation, and capillary and alveolar walls were congested. The liver cells were finely vacuolated throughout the entire lobule with a moderate increase of lymphocytes in the portal spaces. The Malpighian bodies of the spleen were large and numerous. The centers were composed of large pale endothelial cells with peripheral zone of similar cells and small lymphocytes. Lymph nodes were large with hyperplasia of the germinal centers. There was a marked increase in the size of the primary follicles of the intestine, which were composed of large pale cells. The splanchnic ganglia showed a slight increase of connective tissue and irregular nerve cells, some lacking nuclei. The skin showed marked hyperpigmentation in the lower layer of the epithelium with occasional melanoblasts in the underlying connective tissue. No evidence of a calcified mass was found on serial sectioning of the brain. There was slight but definite meningoencephalitis in the hypothalamus, with one small perivascular hemorrhage and an exudate composed mainly of lymphocytes.

Sections of the adrenal showed a complete absence of cortical tissue, this being replaced by dense connective tissue, which was infiltrated diffusely and focally with lymphocytes (Figure 6). The medullary tissue was also reduced in amount. Around the surviving medullary cells was a massive infiltration of lymphocytes, surrounded by fibrous tissue and a thin layer of collagen and small blood vessels.

The thyroid acini contained a moderate amount of dense acidophilic colloid. The cells were low cuboidal without hyperplasia. Calcification of the internal elastic membrane of the thyroid arteries was noted. Many sections of the thyroid gland failed to reveal any embedded parathyroid tissue.

The pituitary stalk appeared small in diameter. The gland showed no distinct basophilic cells, although an occasional large cell contained a few basophilic granules. The eosinophiles were of usual size and number. The chromophobes were proportionately increased and had abundant cytoplasm.

The lobules of the thymus were distinct and contained a uniform distribution of small round cells without a reticulum. There was an occasional large hyalinized Hassal's corpuscle. The islands and acini of the pancreas were normal; the interstitial tissue showed focal areas of lymphoid tissue. Uterus and vagina were infantile. The acini of the breast were lined with cuboidal or columnar cells without evidence of secretion.

Anatomical diagnoses:

1. Primary atrophy of the adrenal glands with complete destruction of the adrenal cortex.
   Pigmentation of the skin.
   Generalized enlargement of visceral lymphoid tissue.
   Hypoplasia of uterus, tubes, and ovaries.
   Absence of basophilic cells of pituitary.
2. Absence of parathyroid glands.
   Generalized alopecia.
3. Congestion and edema of lungs.
4. Meningoencephalitis of hypothalamic region.
5. Healed ventriculography wound of scalp and calvarium.

DISCUSSION

This patient presented the classical clinical picture of hypoparathyroidism from the age of three years, viz.: tetany and trophic changes—dry rough skin, scanty hair, brittle nails, and poorly developed teeth. At the age of nine and a half years all the criteria of Drake *et al.* (10) for a diagnosis of chronic idiopathic hypoparathyroidism were fulfilled, viz.: low serum calcium, high serum phosphorus, and absence of rickets or renal insufficiency. Calcium therapy alone gave slight improvement of symptoms and blood chemistry; replacement therapy with parathormone resulted in marked increase of urinary excretion of phosphorus, elevation of serum calcium, and depression of serum phosphorus. The earliest evidence of superimposed adrenal insufficiency was darkening of the skin at the age of $10\frac{1}{2}$ years. As the pigmentation deepened, the blood pressure gradually fell, and serum sodium determinations tended to be low. At $11\frac{1}{2}$ years of age she suddenly went into a crisis of acute adrenal insufficiency, with abdominal pain, vomiting, and shock. The value of the serum sodium at this time was 124 m. eq. per liter. Replacement therapy with fluids, sodium chloride, and crude adrenal cortical extract (*Eschatin*) afforded prompt improvement. In spite of a continued high sodium intake, blood pressure declined gradually, and the terminal illness suggested acute adrenal insufficiency.

Thus the clinical diagnoses of hypoparathyroidism and hypoadrenalism were well established and validated by laboratory data. Both diagnoses were confirmed by the absence of parathyroid and adrenal cortical tissue at pathological examination. The additional histological findings of absence of basophilic cells from the pituitary and lymphocytic infiltration of the thyroid gland have been previously described in adrenal insufficiency (11, 25, 43).

In none of the previously reported cases of hypoparathyroidism with autopsy has adrenal cortical atrophy been found. In the two published cases of combined parathyroid and adrenal insufficiency, the adrenal dis-

ease could reasonably be ascribed to an infectious process. One was a 12 year old boy (39) with idiopathic tetany, who developed pigmentation, hypotension, and loss of weight, terminating fatally. A history of pleural effusion and a strongly positive tuberculin test were presumptive evidence of a tuberculous basis for the adrenal insufficiency in the absence of an autopsy. The other patient was an eight year old girl (40) with moniliasis and severe Addison's disease with superimposed hypoparathyroidism. This patient, who is still alive, has not yet been reported in detail. In our patient no evidence of either of these infections was found at necropsy. One other case of hypoparathyroidism in a 41 year old male (44) was associated with increased pigmentation of the skin, but neither further evidence of adrenal insufficiency nor pathological examination was obtained.

It is interesting to comment on the interrelated and perhaps antagonistic effects of these two glandular deficiencies. Eppinger, Falta, and Rudinger (14) were the first to suggest an antagonistic action of parathyroid and adrenal glands. Guleke's report (17) that in dogs and cats adrenalectomy or ligation of the adrenal veins relieved parathyroprivic tetany, and the finding of an increased concentration of calcium in the serum of totally adrenalectomized rabbits (22), rats (33), and cats and dogs (31, 42) seem to support the theory of antagonism between these two endocrine systems. Taylor and Caven (42) found that parathyroidectomized animals also showed a significant rise of serum calcium after adrenalectomy provided the pre-operative calcium level was above 5 mg. percent. Moreover, they demonstrated that extracts of bovine adrenal cortex caused a 15 to 30 percent depression of serum calcium in rabbits. The latter finding was confirmed by Mirvish and Bosman (29), who controlled their observations by injections of extracts of other tissues without obtaining any fall in serum calcium in the control animals. Adrenal insufficiency and excess of parathyroid hormone have a number of similar effects, viz.: congestion of intestinal mucosa with hemorrhage (8, 32); changes in water and electrolyte metabolism—dehydration, oliguria, azotemia—responding in both instances to the same treatment of replacement of water and electrolytes (37); and similar changes in the teeth of rats (35, 36). On the other hand, Harrop and Soffer (18) obtained no significant increase in serum calcium in their dogs with experimental suprarenal insufficiency. Grollman (16) concluded after discussing the experimental reports that there was no valid evidence of an intimate adrenal cortical-parathyroid relationship.

Too many variables were present in our patient to draw conclusions. Although during the last six months of life she had no signs of tetany and did not require parathormone therapy, she was then receiving in addition

to a high calcium, low phosphorus diet extremely large supplements of calcium lactate. Moreover, her serum calcium remained low, and she had four convulsions in the seven weeks following her first attack of acute adrenal insufficiency. Evidence, therefore, of an ameliorative effect of adrenal insufficiency on the clinical course of chronic hypoparathyroidism is lacking.

It seems worthwhile to comment on some of the infrequent complications of hypoparathyroidism manifested by this patient. One of these was increased intracranial pressure with papilledema, regressing with specific therapy. Albrecht (1) in 1924 collected eight similar cases from the literature and reported one of his own. Barr (4) reported two cases, one in parathyroprivic tetany, the other in idiopathic hypoparathyroidism. He speculated on the possibility that the normal level of spinal fluid calcium in the presence of low serum calcium levels might contribute to accumulation of cerebrospinal fluid during tetany and to its disappearance after treatment. Seven additional cases with similar findings have been reported (20, 29, 38, 39).

An unusual roentgenographic finding was diffuse symmetrical calcification throughout the brain substance. Such calcification had been described at autopsy in the German literature, but its ante-mortem recognition in three cases was first reported in 1939 by Eaton and Haines (12), and two similar case reports have appeared subsequently (10, 34). It begins as colloid deposit in and around the finer cerebral blood vessels, with subsequent calcification. Mental retardation, as in our case, is a frequent concomitant.

Another unusual feature was acute keratoconjunctivitis, with marked photophobia and lacrimation, running a prolonged course. Two similar cases have been reported in association with idiopathic hypoparathyroidism (13, 39). In these cases, however, tuberculin tests were strongly positive, in contrast to the negative test in our patient.

SUMMARY

1. A case has been reported in which adrenal insufficiency developed in the course of chronic idiopathic hypoparathyroidism. Necropsy established almost complete absence of adrenal cortical tissue and no demonstrable parathyroid tissue.

2. The experimental evidence bearing on the reciprocal relationship between the parathyroid and adrenal glands has been reviewed.

3. In addition to the classical features of both deficiency syndromes, manifested by this patient, other less common findings of chronic hypoparathyroidism included increased intracranial pressure with papilledema, calcification in the brain substance, and keratoconjunctivitis.

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ADRENOCORTICAL CANCER WITH UNDULATING FEVER IN ADDISON'S DISEASE

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THE following observation helps us to elucidate certain points in the natural history of Addison's disease, particularly the rôle of adrenocortical cancer in the genesis of this disease and the significance of undulating pyrexia in the Addisonian clinical picture.

CLINICAL OBSERVATION

G. P., 34-year-old male, was observed principally during the first four months of 1945. His whole history can be divided into five phases, (a) a prodromic phase: (b) a phase of onset of distinct symptoms, (c) a phase of severe Addisonian crisis, (d) a phase of subacute Addisonism, and (e) a terminal phase of Addisonian coma.

Personality, constitution. The patient was a Greek from the Greek islands. There was nothing particular in his heredity nor in his previous history save for an appendectomy done in 1940. He complained at that time of vomiting and pains. The appendix showed chronic lesions.

Physically he was a "pycnic," brevilinear, of normal stature, muscularly powerful, violent and a little aggressive. He had a tendency to overweight, weighing more than 12 stone in 1943. His blood pressure, taken during a health examination in 1940, was 100/70. His blood group was O. In his early youth he had joined the Merchant Navy and had travelled extensively. He was successful in business, active and extrovert, keen on amusing himself and gambling. He was happily married, but his wife and child were cut off from him, as they were in Athens during the occupation of Greece, and this worried him intensely. He was rather hypersexual but not a heavy smoker nor drinker.

Prodromic phase, 1942–November, 1944. Towards the beginning of 1942 the patient had vague symptoms of asthenia and occasional vomiting. He also had sudden atacks of mental depression. In his own words, "I used to be taken with profound melancholy. I used to cry without any cause or explanation." He was treated for "dyspepsia," "nicotine poisoning," "neurasthenia and hypotension." He took some "slimming pills" (thyroid) for a long time. He was in fact rather obese and at the same time muscular. There was no diminution of potency.

Onset of characteristic symptoms, November, 1944–January 11, 1945. In November, 1944, he entered University College Hospital because his depression and vomiting had become accentuated. Clinical and radiological exploration of the digestive and respiratory systems was negative, and findings were normal in the nervous, circulatory and urinary systems. Electrocardiogram normal. Pressure not noted. Urine showed no albumen. Blood showed polyglobulin, to which little attention was paid. Erythrocyte count was 7,200,000 per cu. mm., with 90% haemoglobin. Leucocyte count was 6,000 with polymorphs 34%, lymphocytes 56%, and mononuclears 10%. Blood sugar was 111 mg. percent. Blood platelets were 400,000 per cu. mm.; bleeding and clotting times, normal. At onset, temperature was lower than normal, about 97°F., but on November 30 it rose to 100°F.

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The tonsils were incriminated as the principal aetiological factor of the condition, and tonsillectomy was performed on December 7, 1944. After the operation the temperature rose to 105°F. but fell two days later to about 100°F. Bronchopneumonic symptoms developed; asthenia and vomiting became accentuated. He was seen in consultation with Dr. Cawadias on January 9, 1945. Diagnosis: Addison's disease in a condition of crisis (post-operatory); bronchopneumonia.

Addisonian crisis, January 11–15, 1945. The patient was transferred to the London Clinic. The condition was rapidly becoming worse. Mental confusion was verging on coma. Vomiting was intense. Heart was normal, but pressure was 55/35 mm. Hg. Cough and expectoration with râles on the right base were present. There was an intense pigmentation of the skin, of "bronzed" type. Large plaques of melanotic pigmentation were present on the buccal mucosa and lips. Temperature was 100°F.; pulse, imperceptible. The blood showed 5,680,000 erythrocytes per cu. mm. with 60% haemoglobin and marked hypochromasia; leucocyte count was 7,333 with 54% neutrophils, 39% lymphocytes, 6% monocytes. Intensive treatment with adrenocortical extract was instituted (*Eucortone*, 100 cc. per 24 hours with saline infusions and *Redoxon forte* injections). Following this treatment the patient became conscious. Vomiting diminished. Blood pressure on January 13 was 72/10 mm. Hg.

Phase of sub-acute Addisonism, January 15 – April 22, 1945. During this phase the patient showed a general condition of balanced Addisonism interrupted by a few paroxysms. He was maintained by high doses of adrenocortical extract (40–60 cc. daily) with thiamine hydrochloride injections, ascorbic acid and salt. He did not react so well to DOCA. Any diminution of the adrenocortical extract caused aggravation of the condition. In fact we had the impression of dealing with an adrenalectomized animal needing its constant supply of adrenocortical extract. Thanks to the kindness of Sir Alexander Fleming a course of penicillin was instituted in March (1,000,000 units) to determine whether the high temperature was due to a secondary, even undetermined, infection. No result except from a psychological point of view was obtained.

The paroxysms (crises) were brought on by emotional factors (news and thoughts about his family in Athens), by diminution of the adrenocortical extract, once after pyramidon intake and once during a heat wave. During the crises digestive and nervous symptoms were aggravated.

The general course of the Addisonism was as follows.

The general asthenia was constant, and the patient was usually in bed, although comfortable. Wasting was marked only in the last weeks. Pigmentation of the skin improved greatly with treatment but became more intense in the last month (April) notwithstanding treatment.

The whole course was febrile. Hyperthermia occurred in the form of "undulating fever." These waves occurred during the whole period when he was under our observation. They were separated by very short intervals (1–3 days at most) of normal temperature. They were not very regular. At onset the crest of the wave reached 101–102°F. Later it could reach 104°F. Only two rigors were noted. There was no perspiration. The pulse was not accelerated in relation to the elevation of temperature. With 103°F. the pulse rate was 100 per min., with 104°F., also 100 per min. The severity of the symptoms was not parallel with the temperature, and in many instances the patient felt well notwithstanding very high temperatures. Respirations were between 24 and 32 per min.

Blood cultures were negative. Cultures from the throat showed neither haemolytic streptococci nor any other pathogenic micro-organism. The only bacteria present were those normally present in the throat. Quantitative tests showed a slight increase in the

number of pneumococci, but otherwise the relative numbers of bacteria were normal. All agglutination reactions were negative.

A further careful search for any pathogenic micro-organism, made in Sir Alexander Fleming's laboratory at St. Mary's, was negative. Penicillin did not influence the temperature.

The mental status showed important features. There was a definite change of personality. The patient became anxious about money matters, and ideas of ruin filled his mind (although in fact he was very wealthy and before his illness spent freely). He was emotional but not definitely discouraged or aboulic. Mental paroxysms occurred without any particular reason, taking the form of apathy, confusion, excitation or hallucinations. During the attacks of apathy he was indifferent to his environment, he did not answer questions and was not interested in seeing anybody. From apathy he would pass into confusion with disorientation. Hallucinations were a striking feature. He would go to the window and point out to the nurse imaginary men walking on the roof of the house opposite. Twice he told me that he had seen a man stab another in the street. On April 2 he dressed himself and wanted to leave the nursing home because he was seeing serpents in his room and the nurse was giving him "electric currents." He insisted on changing the bed clothes because "the nurse was always putting him on a rubber sheet." He complained of a peculiar smell which he could not define but said was due to the fact that they were bringing him things from the theatre (the mouse smell described in Addison's disease did not occur). Twice he got up at night and tore up pound notes.

The heart remained normal during the whole period except for extra systoles, which occurred in March. Pressure was well maintained at 90/50 mm. Hg. Pulmonary symptoms of cough, expectoration and râles continued. There was no Koch's bacillus in the sputum.

The urinary system, apart from water retention, showed no abnormality. There was a faint trace of albumen in the urine and a slight centrifugal deposit containing a few granular casts, detached renal cells and isolated blood discs. No leucocytic excess and no crystals.

The digestive symptoms consisted principally in vomiting, usually without effort. This occurred in bouts but was rare during treatment, and the patient could take substantial food, especially as his appetite was good except during rare periods of anorexia. On three occasions he had hiccups lasting two to three days. Stools were fairly normal.

The erythrocytic syndrome showed interesting developments, and a hypoglobulin and hypochromic anaemia, masked at onset by the haemoconcentration, became manifest. The red cells, which during the initial crisis were 5,680,000 per cu. mm. diminished progressively. January 31, the erythrocyte count was 4,400,000 per cu. mm. with 80% haemoglobin; on April 24, 2,480,000, with 36% haemoglobin. Hypochromasia, anisocytosis and poikilocytosis were marked. Sedimentation rate on January 30 was: one hour, 130 mm.; two hours, 140 mm. (Westergreen); on March 28, one hour, 60 mm. Transfusion was considered but rejected for fear of untoward reactions.

The white cells also showed various changes. On January 16 the leucocyte count was 9,600 per cu. mm.; polymorphs, 48%; lymphocytes, 45%; hyalines, 0.4%. On January 31, the leucocyte count was 22,000 oer cu. mm.; polymorphs, 62.5%; lymphocytes, 29%; hyalines, 0.5%. In February, the leucocyte count was 10,500 per cu. mm.; polymorphs, 55%; lymphocytes, 42%; mononuclears, 2%; eosinophiles, 1%. On April 24, the leucocyte count was 12,900 per cu. mm.; polymorphs, 59%; lymphocytes, 36%; monocytes, 4%; eosinophiles, 1%. This polynucleosis corresponded to the pulmonary symptoms, and up to a certain point to the fever.

The study of the fluid intake and urinary output in January and February showed retention of water, the output being from 300 cc. to 900 cc. (10 to 30 ounces) less than the intake.

The metabolic syndrome, which could not be studied thoroughly owing to the condition of the patient, is indicated by the following figures.

Sugar in blood	16.1.45	111 mg. per cent.
Urea in blood	5.4.45	101 mg. per cent.
Creatine in urine	20.1.45	200 mg. per cent per 24 hours.
Creatinine in urine	20.1.45	1,340 mg. per cent per diem.
Sodium in blood serum	5.4.45	294 mg. per cent.
Chlorides in serum	5.4.45	549 mg. per cent.
Sodium in urine	20.1.45	422 mg. per cent in 24 hours.
Potassium in blood	5.4.45	21.2 mg. per cent.
Porphyrin in urine, test positive, but no spectroscopic evidence of haematoporphyrin.		

Terminal syndrome. Despite continuation of intensive treatment with adrenocortical extract the condition deteriorated gravely and nearly suddenly in the second fortnight of April. The patient entered into deep coma on April 22 and died on April 25. Hyperthermia persisted to the end.

To sum up, a "pycnic" individual, aged 34 years, showed for nearly two years occasional symptoms of depression, weakness and vomiting. In the last two months asthenia and vomiting became accentuated, and pigmentation and polyglobulinaemia occurred. After tonsillectomy there was a typical Addisonian crisis of comatose form from which he recovered, thanks to intensive adrenocortical extract therapy. After that, for three and a half months a severe Addisonian syndrome developed, interrupted by paroxysms. Leading symptoms were intense skin and mucosal pigmentation, asthenia, hypotension (corrected up to a point by treatment), attacks of vomiting and hiccough, attacks of hallucinations, hypoglobulinic and hypochromic anaemia, and an intense undulant fever. Blood sugar and electrolytes were maintained at fairly normal figures. Without any special occasional cause, life terminated in coma.

Anatomopathological Examination

Autopsy was performed by Dr. Neumark (St. Mary's Hospital Pathological Laboratory). The pathological examination was made by Professor Newcomb and Dr. Neumark.

Cardiovascular system

There was a brownish color of the myocardium. The endocardium and valves were clean. All chambers contained post-mortem clots. Slight atheroma were in the aorta. Histologically there was some brown atrophy.

Respiratory system

Macroscopically there was some chronic bronchitis. The lungs showed some emphysema macroscopically. There was bronchopneumonia with much pulmonary oedema microscopically. Pleura was clear except for slight right basal adhesion.

Alimentary system

Nothing abnormal in oesophagus, stomach, or intestines. The para-aortic lymph glands were enlarged, whitish, soft. Macroscopically chronic inflammatory reaction. Liver had a nutmeg pattern; was rather fatty at periphery of lobule. Microscopically there was an in-

crease of peripheral fat in hepatic lobules. There was a small gland at the junction of hepatic and cystic ducts. Microscopically this showed inflammatory changes, and on the peripheral sinus there was a small collection of cells resembling those found in the adrenal tumour. The gall bladder contained dark green bile; the ducts were patent. The pancreas was normal.

Left suprarenal

This measured 6.5 cm. ×4 cm. ×3 cm. It was a hard, well-encapsulated mass, and had no resemblance to the suprarenal except its shape. On section it had a similar appearance to the mass on right kidney. Microscopically there was very little resemblance to a normal adrenal. There was extensive necrosis, some fibrosis and, between the fibrous tissue cells, there were collections of cells arranged mainly in trabecular fashion, and some were in alveoli. There were no tubules. These cells varied in size and shape. Most were anaplastic, some possessing more than one nucleus. Some were almost spindle-shaped, others globular. Some stained intensely black with Weigert's haematoxylin, but others did not take up the stain. Mitotic figures were not numerous. Sections frozen and stained with Sudan III and haematoxylin showed that the centre of the adrenal contained much fat, but fat was not a prominent feature of the tumour cells.

Right suprarenal

This was an irregular mass, partly broken up, and was removed with difficulty. It measured about 4 cm. in diameter. Its microscopical appearance was similar to that of the left suprarenal, but it was more necrotic.

Left kidney

This measured 10.5 cm. ×5 cm. ×4 cm. Microscopically it showed ischaemic fibrosis.

Right kidney

This measured 12 cm. ×6.5 cm. ×5 cm. The upper pole was replaced by a mass of about 5 cm. diameter, which on section was definitely circumscribed. The mass was hard, whitish yellow, somewhat whorled and broken down in parts. Microscopically this tumour was not encapsulated and consisted of tissue like that described for the adrenals (principally the left adrenal, as the right adrenal was very necrotic). There was much necrosis. Staining with Sudan III showed the same distribution of fat presented particularly by the left adrenal. This tumour pressed on the liver, but as shown by microscopical examination, although it compressed the liver lobules, it did not invade them.

The diaphragm showed a great deal of fibrosis but no invasion by the tumour. Although there were many collections of small round cells in the muscle and even on the pleural surface, no tumour cells were found in these sites.

The spleen was septic, with many polymorphs and a good many eosinophiles. Prostate was normal. The nervous system, thyroid and pituitary were not examined.

Pathological diagnosis. Professor Newcomb, who examined these preparations together with Dr. Neumark and myself, concludes that this is a case of carcinoma of the adrenals with metastases in the right kidney.

DISCUSSION

Three important points in the natural history of Addison's disease have to be considered on the basis of this clinical study combined with the critical evaluation of allied observations.

The possibility of adrenocortical carcinoma as a cause of Addison's disease.

Addison considered that cancer could give rise to the disease he had described. Wilks, however, and principally Greenhow rejected this etiology. In his Croonian lectures at the Royal College of Physicians in 1875 Greenhow (5), after discussing the cases reported as cancer of the adrenals giving rise to Addison's disease, rejected all of them. Three of the cases cited, however, appeared to him of difficult interpretation, and he wrote, "If these three cases were in truth cases of cancer of the suprarenal capsules they are the only cases on record in which cancerous disease of these organs has ever given rise to the constitutional symptoms and bronzing of the skin characteristic of Addison's disease." This opinion has prevailed, and Rowntree and Snell (10) write in their classical monograph that carcinoma is "a negligible consideration in the cause of Addison's disease."

I believe that this conception should be changed, and the possibility of rare cases of Addison's disease due to cancer of the adrenals should be accepted. In fact, in 1908 I communicated with Galliard (4) a case of acute Addison's disease in which autopsy showed carcinoma of one adrenal gland and distinctive lesions of the adrenocortical tissue of the opposite gland. In 1909 Winkler (12) recorded two cases of fully developed Addison's disease associated with cortical tumours of the adrenal gland. In 1930 Anderson (1) reported a case of fatal hypoglycaemia in which the blood sugar dropped to 0.04 per cent before ending in hypoglycaemic coma despite the use of glucose and epinephrine, and in which a tumour was found in the left gland, the right gland being "smaller and more fibrous than usual." In 1940 McGavack (6) described a case of of masculinisation terminating in a fatal "Addisonism" and malignant cachexia. Autopsy showed a massive masculinising primary carcinoma of the cortex of the adrenal gland with apparently complete destruction of all normal glandular tissue, moderate atrophy of the left adrenal gland and metastases to the liver, lungs and pleura.

The observation forming the basis of this paper is a further demonstration of the possibility of cancer giving rise to Addison's disease, and probably represents the most complete case described. It should be remembered that there are also rare cases of malignant phaecochromocytoma giving rise to Addison's disease, as shown by McGavack (7). Cases, also reputed to be Addisonian have been described as caused by tumours involving the solar plexus, Fowler (3), Bucknill (2), but as far as I can gather from these observations they were of cases of melanodermia and not of real Addison's disease. Secondary cancer of the adrenals can give rise

also to Addison's disease according to some authors, but more clinical work is necessary to clarify this point.

Fever in carcinogenic Addison's disease

We can go a step further and consider that fever is often characteristic of such Addisonian adrenocortical cancer. An undulating pyrexia of four months' duration was a characteristic of our case. Fever has been described in adrenocortical cancer in general. The case of Trémolières and his collaborators (11) developed as a severe septicaemia. At autopsy a bilateral adrenocortical carcinoma with multiple metastases was found. McGavack (6) also cites cases with fever in his non-androgenic adrenocarcinomas. René Puig (8) described a case developing as an "undulant fever" and shown at autopsy to be a bilateral adrenocortical carcinoma with multiple metastases. It is interesting to compare these observations with that of Roch and Bickel (9), who observed in a woman operated for carcinoma of the breast an "undulant fever" occurring four months after the operation and lasting for six months. Many years ago I observed a case of left hypernephroma with distinct "undulant fever" [*sic.*] in the Evangelismos Hospital of Athens. At first the enlarged left kidney was taken for an enlarged spleen, and the first diagnosis was one of Brucellosis (Mediterranean fever).

In all published observations of adrenocortical carcinoma with fever no agent of secondary infection was found, and in our case in particular a very careful search was made. It is probable that fever in these cases is due to absorption of necrotic tissue. In fact in all observations, including our own, necrosis was a prominent pathological finding.

Addison's disease is usually afebrile or hypothermic. High temperature before death has been described, however, and some clinicians mention cases with "unexplained pyrexia." McGavack writes that Addison's disease should be considered in the differential diagnosis of cryptogenetic fevers. At all events, in cases of Addison's disease with fever the cancerous etiology should be considered.

The mental syndrome in Addison's disease

Descriptions of the psychological manifestations in Addison's disease do not seem to be very complete. Discouragement and depression are described. A more careful investigation in our case showed changes of personality, attacks of unexplained melancholia preceding other symptoms by a long time, and hallucinations. Clinical science would gain by a more precise investigation of such psychological features, because the cerebral cortex seems a very delicate register of metabolic disturbances. It is true that all psychological manifestations in endocrine diseases are not of

purely endocrine-metabolic origin. The psychological personality of the patient enters into consideration, as much is due to his particular psychogenic reactions.

Treatment was of course of no avail. However, adrenocortical extract maintained a survival of the same form, as it maintains the survival of adrenalectomized animals. The electrolyte metabolism was normal even a few days before death, and blood sugar was normal even during the initial severe Addisonian crisis. This is one more argument for accepting that an important and hitherto unknown factor in the adrenal cortex distinct from the electrolyte, carbohydrate and genital factors is responsible for "survival" and that deficiency of this factor in adrenalectomy and Addison's disease causes death.

ACKNOWLEDGEMENT

I am very grateful to Sir Alexander Fleming, F.R.S., Professor W. D. Newcomb, M. D. and Dr. E. Neumark for the help they gave so freely in this case.

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Letters

To the Editor:

A NEW SIGN OF THE CLIMACTERIC

IN EXAMINING women in the climacteric with rheumatic complaints I regularly found tenderness over the lower third of the tibial surfaces. It is limited to the anterior surface of the tibia, not involving the soft tissues about the shin bone. It is a type of hyperalgesia found in bones, not superficial but brought out immediately by adequate pressure. It develops after moderate pressure is steadily maintained. This tenderness begins in the upper portion of the distal third of the lower leg and increases in intensity toward the ankle. The ankle joint is not tender. The tenderness varies, occurring with light pressure in some, but requiring firm pressure to elicit it in others. The degree of tenderness is somewhat more marked in women with other menopausal complaints such as well developed hot flushes. I have found it in menopausal women two months after the last period and in women of eighty years. It has developed as early as three days after castration.

I have never found it in regularly menstruating women, in women with irregular menstruation, nor in women with amenorrhea resulting from pregnancy or wasting disease. It is not related to deformities, varicosities nor edema. It is unrelated to the arterial blood supply, being found in those with pulsating dorsalis pedis and posterior tibial arteries as well as in those without pulsation in their feet or ankles. It occurs in women without any signs of subvitaminosis as well as in those with bleeding gums, low ascorbic levels in the blood, fissures at the angles of the mouth and neuropathy due to lack of thiamin. Administration of thiamin, ascorbic acid or vitamin D does not affect the tenderness. It is neither improved nor made worse by taking 1.5 mg. stilbestrol daily nor by the injection of 20,000 international units of estrogenic substance weekly. It is found in women of all economic strata, and in idle as well as in working women. It is present in negresses as well as in white women. It is not affected by lying in bed for months. Massage does not abolish it, nor does changing the type of shoe. It occurs in the thin as well as in the obese. I have never found it to disappear nor change in intensity. X-ray has not demonstrated any change in the tissues of the lower leg nor in any other part of the skeleton. There is no evidence of Paget's disease.

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Lower tibial tenderness is frequently but not necessarily associated with tenderness of the sides of the cervical vertebrae and tender pads over the medial surfaces of the knees. More commonly found in women having flushes, its intensity parallels the severity of the flushes. Women with plump legs usually have greater tenderness. Estrogenic substance which abolishes the flushes does not affect the tibial tenderness. It is the first physical finding in women in the menopause. I have been unable to find any previous reference to this physical finding of the menopause.

I examined 205 women between 15 years and 79 years of age. Eighty-eight women have experienced physiological or artificial menopause. Those younger than 42 years exhibiting the tibial sign had been castrated by surgery, x-ray or radium. Of the 88 women 64 (77 percent) had tenderness more or less marked in the lower third of the anterior tibial surface. In six regularly menstruating women under 40 years of age, three showed anterior tibial tenderness to a slight degree. These three women were 31, 38 and 39 years old.

I found this tenderness of the lower third of the tibia twice in 41 men varying in age from 37 years to 79 years and twice in 117 men between 20 and 40 who were hospitalized for a variety of illnesses unrelated to leg inflammation.

SUMMARY

Tenderness of the anterior lower third of the tibia has been found in 77 percent of women who have menopausal amenorrhea. This sign has never been observed in menstruating women nor in amenorrheic states not due to menopause. It was observed in three men, two aged 66 years and one aged 72 years.

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TO THE EDITOR:

A SIMPLE TEST FOR HORMONE DEFICIENCY IN THE MALE

THE existence of a state designated "The Male Climacteric" has been pretty well established. The term 'state' is used advisedly for it is more of a status or condition than a pathological syndrome. Were it a syndrome the findings would be more constant. Clinical evidence would

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follow a more constant pattern. Such is not the case. There are few things that give a more varied picture. It seems to fulfill the condition laid down in the aphorism. "The only thing typical about it is that it is always atypical."

Obviously the diagnosis of this thing is very difficult. Unless one is 'climacteric conscious' it will very often be missed. For all intents and purposes it may be considered a deficiency state. Whether it is the actual depleted supply of testosterone or the unbalanced excess of a pituitary hormone produced in the absence of androgen inhibition is not clear, though the former seems more likely. At any rate **the one constant factor is hypogonadism of varying degree.** The widely diversified 'symptoms' vary in severity and quantitatively with the degree of deficiency.

In the light of the foregoing it is readily seen that androgen deficiency is pathognomonic. If the laboratory could qualitatively if not quantitatively demonstrate this, what a boon it could be! The actual 'climacteric' is believed to occur at more advanced age in men than women. Usually it is from 60 to 65 years. There is no doubt that there are many cases where deficiency exists at almost any age with varied, diversified manifestations, heretofore undiagnosed. These cases drift along until someone with a 'hunch' administers testosterone as a therapeutic test.

This is not a very satisfactory method, for the material is as yet too expensive. The androgen level can be determined from the urine but it is a highly technical process. Only an occasional research laboratory has the equipment, knowledge, skill or inclination to conduct this test. If a simple inexpensive test could be performed, not too time consuming to be done in the office of the busy practitioner, it would be a boon to many suffering males and enable us to relieve a very real suffering, perhaps more prevalent than we had dreamed.

It is believed that such a test has been found. It has not been subjected to a sufficient number of trials finally to establish its worth. It is herewith submitted in order that others may try it so as to ascertain if the same results may be obtained in their hands and thus finally prove or disprove its accuracy and value.

The distal portion of the male urethra widens to form the fossa navicularis. The mucosa becomes low columnar to cuboidal with small but very distinct nuclei. They continue distally to form the lips of the meatus whereupon they blend into the more squamous cells of the glans. These low columnar and cuboidal cells are almost identical in appearance and staining reaction to the lining cells of the vagina.

It is well established that the vaginal cells undergo very definite morphological changes due to the degree of presence or absence of estrogen. It now appears that these meatal cells and those of the distal part of the

fossa navicularis in the male urethra undergo very similar changes due to the degree of presence or absence of androgen.

A very simple staining technique demonstrates this. The slide is stained with the Shorr technique in exactly the same manner that a slide is stained from a vaginal smear. When studied under the microscope, the similarity is so great that it would be difficult to differentiate it from a vaginal smear similarly stained. The entire process can be done in five or six minutes and is as follows: the lips of the meatus are held open and a clean, dry glass slide is pressed against their inner, moist surface, and before it has time to dry, it is immersed in a solution of half ether and half ethyl alcohol. It is allowed to remain in this fixing solution for two or three minutes. It is important that the slide be fixed at once before it drys. It may be stained immediately or at some later time. The specimen is covered with Shorr stain for two minutes. After this it is blotted dry and dipped ten times in seventy percent alcohol, drained, and dipped ten times in ninety-five percent alcohol. The next step can be done in either of two ways. If absolute alcohol is available, it may be dehydrated by dipping it ten times in absolute alcohol. Since this is not always available, it has been found quite satisfactory to dip it into xylol and then blot it dry. Dip it into xylol and blot it dry again repeating this process several times until the xylol appears as an even film over the slide indicating its complete dehydration. The slide is then wiped dry except over the specimen. Whereupon a drop of balsam and a cover glass are placed and the slide is ready for microscopic examination.

The slide of a normal individual will appear as masses of cuboidal cells with very distinct brown staining nuclei and a rather pink staining cytoplasm. These cells are normal and resemble the normal cells of the vaginal epithelium. If, however, there is a hormone deficiency, many or all of the cells will have a distinctly blue staining cytoplasm with a very distinct red nucleus. These are the undeveloped cells and their presence represents the deficiency of androgen in the male just as their presence represents a deficiency of estrogen in the female.

This simple test has been applied to numerous males of varying ages, and in every case where the test denotes deficiency, there was alleviation of symptoms upon the administration of androgen. When adequate amounts of androgen had been administered, in each case, the blue cells disappeared leaving the normal picture.

SUMMARY AND CONCLUSION

First: The distal cells of the male urethra are similar to those of the vaginal epithelium.

Second: These cells differ in their reaction to the Shorr stain with the degree of presence or absence of androgen.

Third: This is a simple procedure for diagnosing hormone deficiency in the male as well as in the female.

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TO THE EDITOR:

EARLY PRODUCTION OF STEROID HORMONE BY TROPHOBLAST

A QUESTION under discussion at the present time is how soon after fertilization can both ovaries be ablated without terminating gestation in man. This presumably depends on the capacity of the conceptus to produce a sufficient concentration of steroid hormones to maintain the integrity of the uterus. It may be interesting in this connection to offer some observations which we made while studying transplantation of human placenta into the anterior chamber of the eyes of rabbits. We found that placental fragments measuring about 1 mm.×2 mm., obtained from the spongy layer, and which contain a small proportion of the steroid-forming syncytial trophoblast are producing sufficient hormone by the 17th day to enable the male host rabbit's urine to cause definite hypertrophy of the uterus of a Friedman doe. Similar observations were made on the uterus of rabbits bearing the eye transplants.

In one rabbit, the growing trophoblast, when transplanted into the anterior chamber of another rabbit, measured about 3.0 mm.×3.0 mm. ×0.3 mm. at the end of 21 days. These observations suggest the possibility that a trophoblast when still very small produces relatively large amounts of hormones effective upon the uterus. They are reminiscent of results obtained by workers with trophoblast producing gonadotrophin when cultivated *in vitro*.

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News Item

A letter has been received from Dr. Raymond Greene of 148 Harley Street, W.1., London, England, in which he announces the formation of a Section of Endocrinology at the Royal Society of Medicine of London. Sir Walter Langdon-Brown is to be the first president; Dr. H. Gardiner-Hill and Mr. L. R. Broster will be vice-presidents. Dr. P. M. F. Bishop will act with Dr. Greene as joint secretary.

Dr. Greene cordially invited members of the *Association* who visit England to feel free to get in touch with him, and he hopes that when travel becomes easier, closer contact between endocrinologists in the two countries will be facilitated.

Book Review

GOLDZIEHER, M. A. *The Endocrine Glands.* New York, Rudolf Schick Publishing Co., 1946, 49 pp., 5 charts.

This forty-nine page, paper-bound booklet contains concise and well written descriptions of the better known facts about the endocrine glands. It is organized in such a way that it would be suitable for a text for nurses, technicians, and anyone who needs a quick review of this subject.

There are five large charts, each measuring 30 × 40 inches which rather cleverly illustrate the functions of the various endocrine glands.—*K.W.T.*

Announcement

SQUIBB AND CIBA AWARDS
ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

The Association for the Study of Internal Secretions has just announced that the award furnished by E. R. Squibb and Sons has been given to Dr. Carl G. Hartman of the University of Illinois, and that the award furnished by Ciba Pharmaceutical Products, Inc., has been given to Dr. Martin M. Hoffman of McGill University.

The Squibb award to Dr. Hartman was based on his fundamental contributions to the physiology of reproduction and the hormonal factors involved in menstruation as well as his fundamental observations on the behavior of insects. Dr. Hartman is Professor of Zoology and head of the Departments of Zoology and Physiology at the University of Illinois. He received his degree of Master of Arts from the University of Texas in 1904 and the degree of Doctor of Philosophy from the same institution in 1915. He was first an instructor and later Professor of Zoology at the University of Texas, from 1912 to 1925; and then a Research Associate in Embryology at the Carnegie Institute from 1925 to 1941, following which he assumed his present duties at the University of Illinois.

The Ciba award to Dr. Hoffman was based on his observations on the metabolism of oestrogens and progesterone as well as those on the excretion of cortin in the urine following trauma. Dr. Hoffman received his degree of Doctor of Philosophy in biochemistry at McGill University a few years ago, and since then has worked as a fellow in the Laboratories of Dr. J. S. L. Browne at Royal Victoria Hospital in Montreal, Quebec, Canada. He is, at the present time, completing his requirements for the degree of Doctor of Medicine. He was only 29 years old at the time the award was made.

Abstracts of

CURRENT ENDOCRINE LITERATURE

Editor; D. A. McGINTY. *Collaborators:* A. R. ABARBANEL, F. N. ANDREWS, B. L. BAKER F. A. DE LA BALZE, ISRAEL BRAM, R. A. CLEGHORN, RUCKER CLEVELAND, C. D. DAVIS ANNA FORBES, M. B. GORDON, H. S. GUTERMAN, M. M. HOFFMAN, R. G. HOSKINS, C. D KOCHAKIAN, H. S. KUPPERMAN, H. L. MASON, JANET W. MCARTHUR, THOMAS H. MCGAVACK A. E. MEYER, K. E. PASCHKIS, A. B. PINTO, J. R. REFORZOMEMBRIVES, E. C. REIFENSTEIN JR., G. G. RUDOLPH, L. T. SAMUELS.

ADRENALS

KUIZENGA, M. H., J. W. NELSON, S. C. LYSTER AND D. J. INGLE. Fractionation of hog adrenal cortex extract. *J. Biol. Chem. 160:* 15–24 (1945).

It was possible to isolate from extracts of hog adrenal glands about six times as much of the compound (17-hydroxycorticosterone) most active in carbohydrate function tests as from corresponding extracts of beef adrenal glands.—*H.L.M.*

RUSSI, S., H. T. BLUMENTHAL, AND S. H. GRAY. Small adenomas of the adrenal cortex in hypertension and diabetes. *Arch. Int. Med. 76:* 284 (1945).

The principal observations generally reported concerning persons with tumors of the adrenal cortex consist of obesity, purple striae of the skin, acne, polycythemia, osteoporosis, imbalance of plasma electrolytes, diabetes, hypertension and genital dystrophy. These signs and symptoms have been observed in persons with adenomas and hyperplasias as well as in those with carcinomas of the adrenal cortex, and the total picture is usually referred to as Cushing's disease or adrenogenital syndrome. The incidence of benign adenomas of the adrenal cortex in 9,000 routine autopsies was found to be at least 1.45 per cent. The incidence was 2 per cent in females and 1.2 per cent in males. There appeared to be a gradual increase in age incidence up to the seventh decade, although this may have been only a reflection of the age distribution of the autopsies as a whole. Hypertension and diabetes occurred five times as frequently in persons with cortical adenomas as in the general autopsy group, and both diseases were frequently present in association with such a tumor in a single person. The relation of the adrenal hormones to diabetes and hypertension was studied, and hypotheses concerning the possible role of the vacuoles and solid cells comprising the tumors in the production and storage of these hormones were formed.—*I.B.*

ENDOCRINE GENERAL

The preparation and biological effects of iodinated proteins:

1. Introduction, by SIR J. BARCROFT.

2. Preparation and properties of physiologically active iodinated proteins, by R. V. Pitt Rivers and S. S. Randall.
3. The effect of iodinated protein feeding on the lactating cow. Part 1, by K. L. Blaxter
4. The effect of iodinated protein feeding on the lactating cow. Part 2, by K. L. Blaxter
5. The effect on basal metabolism of milk from cows fed with iodinated protein, by J. D. Robertson
6. Further experiments on the restoration and maintenance of growth after thyroidectomy, by I. W. Rowlands
7. Use of Rana temporaria tadpoles for the assay of thyroidal activity, by R. Deanesly, J. Emmett and A. S. Parkes
8. Use of Xenopus tadpoles for the assay of thyroidal activity, by R. Deanesly and A. S. Parkes
9. Biological activity of iodinated proteins, by R. Deanesly and A. S. Parkes

J. Endocrinol., 4: 219–356 (1945).

The entire number of the journal is devoted to a report of the work carried on during the war on the use of iodinated proteins to increase lactation in cattle. Iodinated plasma was first tried without significant effect. This was followed by the use of iodinated ground-nut protein which was variable in its influence. Iodinated casein seemed quite effective in increasing lactation. The influence on lactation of the different products was proportional to their thyroid activity as demonstrated by the tadpole test. Milk production was increased during the mid-portion of the lactation period. There was little influence on the early period of lactation and little effect in prolonging lactation. The effect was proportional to the normal milk production of the cow; those showing the highest level of milk production showed the greatest increase with iodinated protein.—*L.T.S.*

Bloch, K. The biological conversion of cholesterol to pregnanediol. *J. Biol. Chem. 157:* 661–666 (1945).

Cholesterol containing deuterium was fed to a woman in the eighth month of pregnancy. Since the pregnanediol glucuronidate isolated from the urine following feeding of the cholesterol contained significant concentrations of deuterium the direct conversion of cholesterol to progesterone, the precursor of pregnanediol, appears to be a normal process.—*H.L.M.*

Carreyett, R. A., Y. M. L. Golla, and M. Reiss. The action of gonadotrophic hormone and of pituitary corticotrophic hormone on the cholesterol content of the adrenals. *J. Physiol. 134:* 210–214 (1945).

The injection of partially purified gonadotrophin from pregnant mare's serum into. male Wistar rats weighing between 30 to 50 gm. increased the cholesterol content of the adrenals. The increase became less on continued treatment and after the third day there was a marked decrease. Corticotrophic hormone prepared from anterior pituitary

on the other hand produced an initial decrease followed by an increase on prolongation of the injections beyond three days. In hypophysectomized rats the injection of corticotrophic hormone produced a further decrease in the already decreased cholesterol content of the adrenal and continued injections produced an increase. These changes are associated with the effect of these hormones on 17-ketosteroid excretion in patients.—*C.D.K.*

COWIE, A. T. AND S. J. FOLLEY. Some factors affecting the absorption rate of subcutaneously planted hormone tablets, *J. Endocrinol. 4:* 375 (1946).

The absorption rate of compressed tablets of hexoestrol prepared by different pressures and of cast and compressed testosterone tablets were studied after subcutaneous implantation in rats. Absorption rate of the compressed hexoestrol tablets was for all practical purposes independent of the pressure used in making them. The material appearing to be highly incompressable. The absorption rate of the cast and compressed tablets of testosterone was similar during the initial period but the rate was maintained somewhat better in the compressed tablet than in the cast. As a whole all tablets tended to obey the law enunciated by Bishop and Folley based on the assumption that absorption rate at any instant is proportional to the surface area at that instant. Addition of 25 to 50 per per cent lactose in the tablet did not hurry the absorption of the hormone. The ghost formation which occurs in compressed tablets apparently occluded the pores and therefore limited absorption to the surface similar to that of the cast preparation —*L.T.S.*

FREED, S. C. Menstrual dysfunctions. Amenorrhea, oligomenorrhea and hypomenorrhea. *West. J. Surg. 54:* 1–9 (1946).

Amenorrhea is classified into hyper- and hypohormonal types. Diagnostic techniques useful in differentiating the sub-varieties of these types are described. The importance of an etiologic diagnosis is stressed and general therapeutic principles enunciated.—*J.M.*

FREED, C. S. Menstrual dysfunction. The climacteric. *West. J. Surg. 54:* 103–109 (1946).

The organic and psychic changes characteristic of the menopause are described in detail. The basic techniques of medical, psychologic and endocrine therapy are reviewed. —*J.M.*

FREED, C. S. Menstrual dysfunctions. Abnormal uterine bleeding. *West. J. Surg. 54:* 45–49 (1946).

The classic types of abnormal uterine bleeding are defined. Estrogen therapy is recommended for excessive uterine bleeding due to hyperestrinism, in preference to gonadotropin, progesterone or androgen therapy.—*J.M.*

GRENVILLE-MATHERS, R. Significance of premenstrual fever in pulmonary tuberculosis, *Brit. M. J. 1:* 523 (1946).

The author studied fifteen healthy young women and found, as reported by others, that in thirteen of the fifteen women there was a premenstrual rise in temperature. This was also found in 43 out of 50 patients with pulmonary tuberculosis. The rise in the latter group tended to be more pronounced and of longer duration than in the normal subjects. It is not related, however, to any increased tuberculous activity. Six patients show-

ing a regular monthly temperature cycle were treated with thiouracil. This eliminated the temperature change. It is concluded, therefore, that the cycle is due to variations in activity of the thyroid gland.—*L.T.S.*

HURWITZ, D. AND D. JENSEN. Carbohydrate metabolism in normal pregnancy. *New England J. Med. 234:* 327 (1946).

Alimentary glucose tolerance curves were run on 25 healthy patients during the first, second and third trimesters of pregnancy, immediately after delivery and several months postpartum. Complete data were obtained in eleven cases while those of the other fourteen were complete except for one or two curves. Fasting, peak and three hour levels were normal, but a large number of the patients showed high blood sugar levels at the two hour period, particularly during the second and third trimester of pregnancy. The two hour blood sugar levels were normal in the postpartum samples. Apparently pregnancy exerts a deleterious effect on carbohydrate metabolism which is shown by slower drop in the blood sugar level after glucose ingestion. The authors warn that the high two hour glucose tolerance level cannot be considered diagnostic of diabetes during pregnancy. On the other hand a high three hour level would be significant. Glycosuria is associated with the high blood sugar levels at the peak and the two hour period. From this fact the authors conclude that pregnancy glycosuria is probably due to a high alimentary hyperglycemia rather than to a lowering of the renal threshold.—*L.T.S.*

JOËL, C. A. Dehydrodoisynolic acid and its clinical use. *Nature 157:* 132 1946).

The continuous oral treatment of fifteen castrates with the synthetic estrogen, dehydrodoisynolic acid, produced repeated hemorrhages within three to six months. Late prolification was produced within fifteen months with total doses of 24–30 mg.; a further total dose of 250–300 mg. of anhydrohydroxyprogesterone linguets produced a late secretory phase. The continued administration of small daily doses (0.5 to 2.0 mg.) during the first fortnight of the cycle proved more effective than a single large dose of 5.5 mg. every third day during the same period. In addition, forty women with menstrual disorders, climacteric symptoms or other indications suitable for estrogen therapy were treated. It can be concluded that dehydrodoisynolic acid is especially effective by mouth.—*C.D.K.*

KONEFF, A. A., M. E. SIMPSON AND H. M. EVANS. Effects of chronic administration of diethylstilbestrol on the pituitary and other endocrine organs of hamsters. *Anat. Rec. 94:* 167–195 (1946).

Adult Syrian hamsters were subjected to heavy estrogen treatment by subcutaneous implantation of 10 mg. pellets of diethylstilbestrol. Various organs were studied after periods of treatment ranging from 3½ to 8½ months. In general, the expected results were observed, namely, retardation of growth, gonadal atrophy, reduction of sudanophilic material in the adrenal cortex, a late reduction in size of the thymus and degranulation of the hypophyseal basophiles. Observations of unusual interest were failure of the anterior hypophysis to enlarge significantly, increase in number of acidophiles in males (no differential counts were reported) a striking hypertrophy and hyperplasia of the cells of the pars intermedia with invasion of other parts of the hypophysis by these cells, and exaggerated formation of "Herring bodies."—*B.L.B.*

LAQUEUR, W. AND H. OVACIK. The hippuric acid-test in pregnancy. *Brit. M. J. 1:* 201 (1946).

The intravenous modification of the hippuric acid test of Quick was carried out in 20 non-pregnant women and 50 pregnant women. For the control group the mean average of hippuric acid was 0.77 gram with a range of 0.41 to 10.1 grams. For the pregnant group, who were all in the last trimester of pregnancy, the average was 0.43 gram with a range of 0.15 to 0.76 grams. These results confirm the findings of Meuwerler that in late pregnancy there is a marked decrease in the excretions of hippuric acid after intravenous injections of sodium benzoate. The generally low output of hippuric acid after sodium benzoate in pregnancy makes this test inapplicable where hepatic diseases are associated with that condition.—*L.T.S.*

PARKES, A. S. Some factors affecting absorption from implanted tablets, *J. Endocrinol. 4:* 386 (1946).

Various modifications of the technique of preparation of tablets for implantation and different routes of administration were studied. Absorption of the active substance from diluted tablets implanted subcutaneously was no more rapid than from tablets of the pure compound. Absorption was retarded by crowding together several pellets into one subcutaneous pocket. Absorption by the intraperitoneal route was at least as rapid, and in some cases much more rapid, than by the subcutaneous route.—*L.T.S.*

PICKFORD, M. AND A. E. RITCHIE. Experiments on the hypothalamic-pituitary control of water excretion in dogs. *J. Physiol. 104:* 105–128 (1945).

The daily urinary excretion of water and the immediate diuretic response to the administration of water and normal saline have been observed in dogs before and after (a) removal of the posterior lobe alone; (b) section of the supra-optic tracts; (c) attempted removal of the anterior lobe alone; (d) simple hypophysectomy; (e) simple hypophysectomy and section of the supra-optic tracts at the same time. After any operation involving the loss of the anterior lobe the diuretic response to water was diminished as compared with the normal. The creatinine and urea clearances also fell. The diuretic response to the administration of normal saline tended to be greater than the response to the administration of water. The blood pressure remained normal. Denervation of the kidneys did not affect the appearance of the changes mentioned. Dried thyroid, anterior pituitary and suprarenal cortical extracts and desoxycorticosterone acetate were not found to restore the diminished water diuresis, nor the lowered renal clearances to normal. After section of the supra-optic tracts or removal of the posterior lobe alone, water diuresis was normal or augmented. The average creatinine clearances lay in the normal range. The diuretic response to the administration of normal saline was greater than before operation. Polyuria may follow any of these operations, even in the absence of the anterior lobe but only after section of the supra-optic tracts was it of fairly long duration.—*C.D.K.*

ROCK, J. Menstruation, its disorders and their treatment. *New England J. Med. 233:* 817–824 (1945).

A brief general discussion of the factors involved in normal menstruation and the various disorders associated therewith, together with their treatment.—*L.T.S.*

SHER, N. Causes of delayed menstruation and its treatment, *Brit. M. J. 1:* 347–349 (1946).

The incidence of amenorrhea in 2,312 women in the auxiliary air services was investigated. Of these, 139 gave a history of amenorrhea dating from their entrance into the auxiliary air force. The author attempted to check the hypotheses advanced by German workers during the last world war for amenorrhea of this type. It was not associated with increased work. A large majority were among individuals engaged in sedentary occupations. Neither was it associated with a deficiency of protein. Psychical disturbance seemed to be the major factor. On the basis of these findings the author treated a series of nine individuals who had been carefully checked for possible pregnancy with cardaminocholinechloride, a powerful parasympatheticomimetic. The psychical factor was controlled by administration of placebos to another group. Seven of the nine cases treated with the drug menstruated between 17 and 96 hours after the onset of treatment. One patient on placebos menstruated after three days' treatment. From the success with the parasympatheticomimetic drug the author advances an hypothesis of the etiology of the condition based upon the emotional importance of the hypothalamus. The data which disprove the work and low-protein theories seem to have been well gathered.—*L.T.S.*

TALBOT, N. B., A. H. SALTZMAN, R. L. WIXOM, AND J. K. WOLFE. The colorimetric assay of urinary corticosteroid-like substances. *J. Biol. Chem. 160:* 535–546 (1945)

A chemical method is described for determination of those urinary substances which resemble certain of the 11-oxycorticosteroids in chemical and biologic properties. It is applicable to twelve to twenty-four hour collections of urine. The method permitted recovery of 90 per cent of 17-hydroxycorticosterone and 17-hydroxydehydrocorticosterone, 45 per cent of corticosterone, 35 per cent of dehydrocorticosterone and 0 per cent of desoxycorticosterone present in the urine in unconjugated form.—*H.L.M.*

TORDA, CLARA AND H. C. WOLFF. Acetylcholine Synthesis. *Science 103:* 645, May 24, 1946.

In view of the relationship of acetylcholine to the activities of the nervous system and to myasthenia gravis, considerable clinical interest attaches to the authors' studies on this substance. They are summarized in these words. "Hormones exert an effect on acetylcholine synthesis. Ether extracts of thymus and pancreas decrease the synthesis, while similar ether extracts of other tissues tested (lymph gland, thyroid, salivary gland, lung, and subcutaneous fat) do not. Since the size of the thymus is regulated by the adrenotrophic hormone of the pituitary gland, this hormone was administered to living animals, and the ability of brain to synthesize acetylcholine was ascertained. Brain from animals injected with the adrenotrophic hormone synthesized more acetylcholine than brain of non-injected animals. Most steroid hormones decreased the amount of acetylcholine synthesized, but estrogenic hormones and Δ^5 pregnenolone increased the synthesis. Thyroxine increased the acetylcholine synthesis, as did epinephrine. The effect of epinephrine in increasing the amount of acetylcholine synthesized may explain why epinephrine increases the effect of acetylcholine in the central nervous system and improves transmission from nerve to the muscle."—*R.G.H.*

THYMUS

CARR, J. L. Status thymico-lymphaticus. *J. Pediat. 27:* 1 (1945).

The author gives a review of the literature and an analysis of 49 cases dying of conditions arising from, or directly associated with, pathological changes in the thymus and lymphatic system; these cases were selected from 520 cases of sudden death in children below ten years of age observed in the past six years at the San Francisco Coroner's Office. The case histories and autopsy reports of 23 of the children are given in detail. The following points are stressed: 1) The thymus weight varies so greatly that the best one could hope to establish is an average weight. 2) The normal thymus weight fluctuates widely with factors such as the constitutional heritage, the state of nutrition, the type of diet, infectious diseases, and the influence of other endocrine glands. 3) The thymus weights of patients who have been ill for various periods of time are much lower than those of normal children who have died suddenly from accidents, murder, acute poisoning, anesthesia and the thymic and lymphatic-system conditions included in the present communication. 4) The 49 cases selected for analysis can be subdivided into the following groups: a) cases of hypertrophy of the thymus resulting in strangulation; b) cases of thymic enlargement, lymphatism and anaphylaxis; c) cases of thymic hyperplasia associated with adrenal insufficiency: d) cases of thymic hypoplasia associated with adrenal hyperplasia; e) cases of hypoplasia of the thymus with hyperinvolution, medullary atrophy and degeneration of the Hassall bodies; and f) cases of status thymico-asthmaticus, a new term devised by the author. The author's description of this condition follows. "Under this heading is presented a series of cases occurring in widely varying age groups where death has occurred from asphyxia and wherein the thymus is enlarged. This enlargement is of lesser degree than in cases dying with acute tracheal compression from an enlarged thymus, and associated with it is an hyperplasia of the lymphoid system which, instead of being generalized, is limited largely to the bronchi and bronchioles. Because the lymphocytic infiltration is in the submucosa, and among the muscle fibrils as well as peribronchial, the term asthmaticus is included. This picture cytologically resembles a developing or existing asthma and the clinical course is differentiated with difficulty from true asthma excepting for the single but very important fact that the status thymico-asthmaticus group show no beneficial response to the injection of epinephrine." The author discusses the theoretical causes of death in lymphatism, and the mechanism of strangulation in hypertrophy of the thymus. An abnormality of the adrenal glands was present in nearly half of the 23 cases reported in detail. The author concludes that the present concept that status thymico-lymphaticus does not exist as an entity can be readily disproved by autopsy studies in any Coroner's Office, and that careful postmortem examinations will result in the recognition of the various types of this condition. —*E.C.R., Jr.*

THYROID

BARR, D. P. AND E. SHORR. Observations on the treatment of Graves' disease with thiouracil. *Ann. Int. Med. 23:* 754–778 (1945).

Thiouracil has been employed as a medical treatment in 100 cases here reported from New York Hospital. In 73 of the 100 cases the drug has produced a satisfactory remission for periods up to 21 months. In 37 of 73 the drug has been withdrawn for two to 16½ months without relapse. In 14 cases the drug did not control the thyrotoxic symptoms or did not maintain the patient in a satisfactory condition. Three deaths from circulatory

complications occurred during the course of treatment. Twenty-six unfavorable reactions were observed during thiouracil therapy, at least five of which are attributable to thiouracil. Two cases of agranulocytosis were encountered. The drug exerted a beneficial influence on the creatine defect and on the tendency of thyrotoxic patients to lose nitrogen, calcium and phosphorus. Disadvantages of thiouracil as compared with iodine therapy are the high incidence of toxic reactions, the long initial period of intensive treatment, and the close supervision necessitated during the subsequent period of maintenance therapy. The ultimate place of thiouracil in the therapy of thyrotoxicosis remains to be determined. However, the authors believe that it may achieve a sphere of special usefulness in the treatment of mild and recurrent cases of thyrotoxicosis and in bad risk cases.—*J.M.*

BEHRMAN, S. Exophthalmos following abrupt discontinuation of thyroid medication for obesity. *Proc. Roy. Soc. Med. 38:* 665 (1945).

A brief case report of exophthalmos following thyroid therapy is followed by a five page discussion on exophthalmos and endocrine disturbance by W. R. Brain, I. Mann, and S. L. Simpson. Exophthalmos ophthalmoplegia may occur of thyrotoxic origin or as the result of thyrotropic hormone action. Thyroidectomy or thiouracil would benefit that of thyrotoxic origin. Thyroid extract might help the patient with myxedema or rapid gain in weight. The pituitary production of thyrotropic hormone might be inhibited by estrogens, androgens or thyroid extract. Of 61 cases seen by Brain, the average age was 50. The condition developed after operation more often in men than in women, and he considers men 36 times more apt to have postoperative exophthalmos than women and feels that the striking sex difference in frequency favors this endocrine factor in etiology, rather than mere weight increase or myxedema. Occasionally good results with as much as 20 mg. of stilbestrol per day were reported. Professor Munn's analysis of 18 cases on etiologic basis showed: 1. Primary deficiency of thyroxine with compensatory excess of thyrotropic hormone secretion (4 cases). 2. Primary excess of thyroxine was initial symptom followed by thyroid atrophy or removal, replaced by excess thyrotropic hormone (10 cases). 3. Excess of both thyroxine and thyrotropic hormone arising simultaneously (4 cases). The clinical characteristics of each group were given. Dr. Simpson cited the psychogenic factors of shock and anxiety in the etiology of exophthalmos.—*R.C.*

BRIGNONE, R. F. Modifications of carbohydrate metabolism in hyperthyroidism. *Rev. Soc. argent. de biol. 20:* 260 (1944).

The author studied the carbohydrate metabolism in dogs made hyperthyroid with thyroid medication and in patients with hyperthyroidism. He found a slight increase in the fasting blood sugar (up to 148 mg. per cent) in 31 dogs treated with desiccated thyroid in doses of 0.5 to 4 grams/kg./day. With larger doses there was, in general, an increase in the fasting blood sugar level, but no constant relation was established between the dose of thyroid and the increase in blood sugar level. Diabetes was never produced. Hyperglycemia induced by the oral administration of galactose reached a maximum earlier in dogs treated with thyroid than in normal dogs. The same result was obtained after the intravenous injection of galactose, but only in dogs treated for eight to 16 days. Glycogen reserves, especially of the liver, were diminished in dogs treated with thyroid; cardiac and striated muscle glycogen was diminished only after prolonged treatment. The

oral administration of galactose was found to produce a more rapid and a greater increase in the blood sugar level of hyperthyroid patients than in normal control subjects.—*F.A.de laB.*

BRUNN, E. Toxic diffuse goiter developing after treatment with thyroid preparations. *Acta Med. Scandinav. 121:* 13 (1945).

Brunn reports 18 cases of thyrotoxicosis developing in patients who were receiving thyroid preparations. In the same period a total of 485 patients were treated for thyrotoxicosis. It appears therefore that patients with thyrotoxicosis due to thyroid therapy represent 3.7 per cent of the total number of patients with this condition. All the 18 patients were women, ten of them in the climacteric age group. In 11 of the 18 cases the thyroid treatment was instituted for simple obesity. Three of the 19 patients showed a familial disposition to toxic diffuse goiter since among their nearest relatives unquestionable instances of this condition were ascertained. Two of the 18 patients had a simple goiter prior to the thyroid treatment, and three had hypothyroidism. Thus, disposition to thyroid disease could be demonstrated in eight patients. Pronounced unilateral exophthalmos was found in four patients. Since this symptom has been described also in three of the previously reported 28 cases of toxic diffuse goiter after thyroid therapy, pronounced unilateral exophthalmos in patients with thyrotoxicosis should raise suspicion of a preceding treatment with thyroid substance. In Denmark the yearly consumption of thyroid preparations amounts to 6,600,000 tablets (1 tablet = 100 thyroid units). This is calculated roughly to be at least five times greater than the amount required by the myxedema patients living in this country. The greater part of the thyroid preparations is probably consumed by other patients, chiefly by those with obesity. Thyroid therapy in obesity always entails a certain risk and is therefore once more condemned.—*Courtesy J.A.M.A.*

DANOWSKI, T. S., E. B. MAN, AND A. W. WINKLER. Treatment of hyperthyroidism with a combination of iodine, thiourea in small doses and desiccated thyroid. *Am. J. M. Sc. 210:* 777 (1945).

The authors have treated 12 hyperthyroid patients with thiourea either alone or in combination with iodine or thyroid. Thiourea was re-investigated during the search for a compound that was free from the toxic manifestations of thiouracil. The only toxic reactions produced by thiourea in the patients studied were mild halitosis, occasional nausea in two subjects, and occasional vomiting in one subject. Patients were found to be quite responsive to thiourea in contrast to experimental animals. The authors conclude: 1) Small doses of thiourea, 0.10 to 0.28 gram, given once daily, usually produce and maintain a satisfactory remission in patients with hyperthyroidism previously treated with iodine. 2) The serum precipitable iodine is commonly depressed to myxedematous levels if these doses of thiourea are continued for some weeks, even before the basal metabolic rate has fallen to subnormal levels; desiccated thyroid, 0.06 gram daily, suffices to restore euthyroid concentrations of serum precipitable iodine. 3) Iodine medication does not inhibit the action of thiourea; whether it delays or whether it accelerates or synergizes the response to thiourea is as yet uncertain. A therapeutic regime for the medical treatment of hyperthyroidism based on these observations is described.—*E.C.R., Jr.*

DE ROBERTIS, E. AND W. W. NOWINSKY. The proteolytic activity of the normal and the pathological thyroid gland. *Rev. Soc. argent. de biol. 21:* 120 (1945).

The rate of proteolytic activity of normal and pathological human thyroid tissue was measured photometrically by the estimation of liberated tyrosine and tryptophane from adesine as a substrate with the phenol reagent of Folin-Ciocalteu. The proteolysis of normal glands resulted in 0.37 to 0.57 mg. of tyrosine and tryptophane (expressed in mg. of tyrosine) per 100 mg. of tissue. In severe toxic goiters the proteolytic activity was 96.4 per cent greater than in the normal glands. In mild toxic goiters, where the symptoms including the basal metabolic rate were reduced by treatment with iodine, the proteolytic activity was decreased to 26.2 per cent below the normal level. In simple diffuse colloid goiters the proteolytic activity was 27.9 per cent below the normal level. In two cases of nodular toxic goiters (toxic adenoma) a difference of almost 100 per cent was found in the proteolytic activity of the adenoma as compared with that of the surrounding thyroid tissue. The importance of the enzyme system in the release of colloid and in the physiopathology of toxic and simple goiters is discussed. The conclusion is drawn that the therapeutic effect of iodine is probably due to the inhibition of the proteolytic enzyme system which is normally responsible for the breakdown of the thyroglobulin molecule; this inhibition prevents the release of the hormone from the follicle. It is assumed that the mechanism of this inhibition is a direct iodinization of the proteolytic enzyme inside the thyroid gland.—*F.A.de la B.*

DI PAOLA, G. AND O. SINISCALCO. Menstrual disorders in hyperthyroid women. *Rev. méd.-quir. de Pat. fem. 24:* 446 (1945).

As a result of analyzing the menstrual disorders of 82 hyperthyroid women, the authors conclude. (1) The wide-spread belief that there is a high incidence of menstrual disorders in hyperthyroidism is not borne out in this series of cases, since menstrual disturbances occurred in only 40 per cent of the patients. (2) Hypomenorrhoea, which is not always due to ovarian insufficiency, is the most common finding in these women; it was present in 60 per cent of the patients with menstrual disorders. (3) Amenorrhea that appears early in hyperthyroidism may be caused by the same psychic factor that sets off the hyperthyroidism. (4) The incidence of menstrual disorders parallels the malnutrition of the patients: 61 per cent of the cases of menstrual disturbance occurred in patients with severe thyrotoxicosis. The authors believe that study of the menstrual cycles in women with hyperthyroidism will give evidence of the action of thyroid hormone on ovarian function.—*J.R.R.-M.*

FISHBERG, ELLA H. AND J. VORZIMER. Effect of pyridoxine on granulopenia caused by thiouracil. *Proc. Soc. Exper. Biol. & Med. 60* (2): 181–184 (1945)

During the course of an investigation of the effect of thiouracil on the BMR of 96 hyperthyroid humans a marked fall in the granulocytic cells of 20 per cent of the patients occurred and there were four cases of true agranulocytosis. Eight hyperthyroid patients which had been receiving the usual dose of thiouracil for approximately eight weeks were given 200 mg. of pyridoxine daily by mouth. The average white counts were increased between 1500–2000 cells per cu. mm. In one patient receiving a 0.2 gm. maintenance

dosage of thiouracil the granulocyte numbers dropped from 3700 to 400 per cu. mm. within two days. The injection of 200 mg. of pyridoxine hydrochloride in four cc. of solution resulted in an increase to 1800 granulocytes per cu. mm. within two hours. Thiouracil was withdrawn, pyridoxine injections were repeated on four successive days and the granulocyte count increased to 4900 cells per cu. mm. It was theorized that the rapidity of action of pyridoxine seemed to indicate that its primary action was to release mature granulocytes into the peripheral blood stream but that the possibilities of its effects on the bone marrow should be studied.—*F.N.A.*

GRAINGER, A., D. A. GREGSON, AND H. S. PEMBERTON. Thiouracil in the treatment of thyrotoxicosis. *Brit. M. J. 2:* 343 (1945).

Of twenty-nine cases of thyrotoxicosis treated with thiouracil, improvement was noted in twenty-two, while twelve were classified as much improved of the twenty-one cases of primary type, improvement was noted in nineteen and of the eight secondary types in two cases only. The chief toxic symptoms noted were faintness, flushing and vague muscular pains in the chest, head and neck. Nearly every case showed absolute granulocytopenia of varying degree, usually from the seventh to tenth day. Cessation of the drug for three or four days was usually enough to cause the count to return to normal and the drug was then started again without untoward effects. Only one case developed a true agranulocytosis although two others developed severe neutropenia. One case of purpura developed which abated on cessation of the drug. One case of drug fever was also observed. Several cases showed rashes. Six cases of essential hypertension were also treated for varying periods with little or no response. Two cases of cardiac failure not due to thyrotoxicosis were treated for thirty days with no apparent improvement. One case of myxedema showed no influence on blood sugar, cholesterol or basal metabolic rate when given thiouracil for twenty-six days.—*L.T.S.*

HOUSSAY, B. A. Thyroid and metathyroid diabetes. *Rev. Soc. argent. de biol. 20:* 179 (1944).

The author has investigated the effect of administration of thyroid on the carbohydrate metabolism of dogs. He found that prolonged administration of thyroid does not produce diabetes in dogs with a normal pancreas, but does produce it in dogs in which the amount of pancreatic tissue has been reduced to 2.5 to 3 grams by surgery. Previous treatment with extracts of the anterior lobe of the hypophysis or with thyroid renders the animals more sensitive to the prolonged administration of thyroid. Diabetes may appear only during the administration of thyroid (this is termed thyroid diabetes); or diabetes may persist in a permanent form after the thyroid medication is withdrawn (this is termed metathyroid diabetes). These disturbances in carbohydrate metabolism are accompanied by lesions in the beta cells of the pancreas which are reversible in the former condition and irreversible in the latter. The secretion of insulin by the glands of these animals was demonstrated by grafting the glands into the neck of diabetic dogs. In the early stages of the lesion insulin protected the pancreas, but in the later stages insulin was ineffective. Metathyroid diabetes can be established in the absence of the gonads, the thyroid or the adrenal medulla; it could not be established in hypophysectomized or adrenalectomized dogs which died in hypoglycemia when treated with thyroid. The administration of thyroid aggravates mild or severe diabetes by intensifying the symptoms, accelerating the course of the disease, and shortening the life of the animal. Metathyroid diabetes has the same characteristics as pancreatic diabetes. In the dog,

total thyroidectomy does not modify diabetes of the total pancreatectomy, metahypophyseal or metathyroideal type.—*F.A.de laB.*

HOUSSAY, B. A. AND J. SARA. Thyroid and sensitiveness to alloxan. *Rev. Soc. argent. de biol. 21:* 81 (1945).

Alloxan was given by intraperitoneal injection, in doses varying from 125 to 174 mg. per kg., to three groups of albino rats: 1) untreated (control) animals; 2) thyroidectomized animals; and 3) animals treated with desiccated thyroid extract for 20 to 29 days. The blood sugar level and the dose that was lethal to 50 per cent of the animals were determined. It was found that thyroidectomy decreases and induced hyperthyroidism increases the sensitiveness of rats to the toxic and the diabetogenic action of alloxan. The hyperglycemia induced by alloxan is often more severe than that observed after pancreatectomy in different species of animals, including the rat.—*J.R.R.-M.*

LONGO, O. F. AND L. MOYANO-LOPEZ. Behavior of the liver in thyrotoxicosis. *Prensa méd. argent. 32:* 943 (1945).

The authors have studied the behavior of the liver in patients with thyrotoxicosis with the following results. (1) There was an alteration in the metabolism of carbohydrate as indicated by the galactose test. (2) There was marked liver insufficiency in 36 per cent of 41 cases studied by the hippuric acid test. (3) There was liver insufficiency in 26 per cent of 13 cases studied by the Quick test modified by the ingestion of glycine. (4) There was a decrease in liver function in 23 per cent of 13 cases as shown by the serum globulin coefficient. (5) If bilirubinemia is considered to be a test of liver function, there was partial insufficiency in 17 per cent of 17 cases. (6) The serum phosphatase values were greater than normal in 29 per cent of 17 cases. (7) Liver damage was indicated in 15 per cent of 26 patients studied by the test of Hanger. (8) There was a fall in the prothrombin values of thyrotoxic patients postoperatively, which was more pronounced when the initial values were low; the levels rose to normal 72 hours after operation.—*F.A.de laB.*

MCARTHUR, J. W., R. W. RAWSON, AND J. H. MEANS. Idiosyncratic febrile reactions to thiouracil: clinical characteristics and possible pharmacologic significance. *Ann. Int. Med. 23:* 915–923 (1945).

Case reports of three patients with thyrotoxicosis who developed fever attributable to thiouracil therapy are presented. The sudden onset of the fever after a relatively constant latent period of ten days, the explosive immediate reaction upon readministration of the drug and the character of the accompanying symptoms suggest that the febrile reaction is a manifestation of true drug idiosyncrasy. Circumstantial evidence is produced to support the theory that capacity to bind proteins is the common chemical characteristic which is responsible for the anaphylactic-like complications of chemotherapeutic agents as well as their therapeutic effect.—*J.M.*

MEANS, J. H. Hyperophthalmopathic Graves' disease. *Ann. Int. Med. 23:* 779–789 (1945).

The author classifies Graves' disease into the following types: (1) classic Graves' disease with ophthalmopathy, thyrotoxicosis and goiter, (2) Graves' disease with thyrotoxicosis but no ophthalmopathy, and (3) hyperophthalmopathic Graves' disease

with (a) hyperthyroidism (b) euthyroidism and (c) hypothyroidism. A detailed review of the literature on the pathological physiology of the hyperophthalmopathic type is presented. The problems of diagnosis and treatment of the hyperophthalmopathic type are discussed with thoroughness and practicality.—*J.M.*

SHIRER, J. W. AND M. COHEN. The effects of thiouracil on the thyroid gland. *Ann. Int. Med. 23:* 790–799 (1945).

Thiouracil was administered to six patients being prepared for thyroidectomy for periods varying from ten days to seven months. Photomicrographs of several of these thyroids are presented, together with those of glands prepared with iodine. The histology of the thiouracil treated thyroid resembled that of the toxic goiter before the days of iodine preparation. There was marked hyperplasia with tall pale cells and large nuclei toward the center of the cell. Grossly, the gland removed after thiouracil preparation was red, moist and friable. Secondary closure of the wound was necessary in two cases because of excessive oozing from the gland. One patient had a moderate postoperative reaction and two had severe reactions with temperatures reaching 105. The basal metabolic rates of these patients were, however, elevated when thyroidectomy was carried out.—*J.M.*

THOMPSON, G. H. Self-induced psychosis with hyperthyroidism complicating manic-depressive psychosis: experimental human hyperthyroidism. *Am. J. Psychiat. 102:* 395 (1945).

A patient with long-standing manic-depressive psychosis decided to commit suicide with thyroid tablets, believing that the intent would not be recognized. Under a dosage of 80 grains daily for six months he lost weight rapidly, became extremely irritable and nervous and with considerable pressure of activity though he remained depressed. He then increased the dosage to 120 grains daily and continued it for another six months. Three weeks after the increase, swelling of the ankles, shortness of breath and general signs of cardiac decompensation resulted. The edema progressed to an incapacitating extent. He became still more excitable and developed delusions of persecution and infidelity of his wife and became markedly antisocial. The schizophreniform disorder was diagnosed "psychosis due to Graves' disease." Enforced discontinuance of the thyroid resulted in remission of thyrotoxic symptoms but the clinical picture of retarded depression remained. This case of experimental hyperthyroidism in man is recognized as somewhat unique but the pathophysiological observations were only sketchily reported.—*R.G.H.*

WOOLLEY, P. V., JR. AND R. W. MCCAMMON. Bone growth in congenital myxedema. The use of serial roentgenograms of the Os radius in diagnosis and regulation of therapy during infancy. *J. Pedat. 27:* 229 (1945).

The authors point out that two abnormalities may be detected in serial roentgenograms of the radius in congenital myxedema: 1) a hard, densely calcified epiphyseal plate which does not resemble that encountered in any other condition; and 2) retardation in the appearance of ossification centers. Administration of adequate thyroid therapy results in an almost immediate resumption of bone growth and changes measurable by x-ray are visible within three weeks; the dense zone of calcification remains only as a scar and a distal band of new bone can be discerned. A curve constructed from some 400

measurements on the radii of babies without evidence of thyroid disease is presented as a standard for the rate of growth during the first two years. The authors stress that this method of measuring thyroid function can be applied to children below two years of age in whom other tests of thyroid function are not easily applicable. They report the histories of three infants with congenital myxedema: 1) an infant who had a well-established deficiency when treatment was instituted and who showed with adequate thyroid therapy changes in the radii which closely paralleled the clinical improvement; 2) an infant with a well-established deficiency who at first received inadequate thyroid therapy and had delayed bone growth which paralleled the lack of clinical improvement but who subsequently responded with bone growth and clinical progress to adequate thyroid therapy; and 3) an infant who was started on adequate therapy before evidence of deficiency was fully manifest and who progressed in every way as a normal child.—*E.C.R., Jr.*

ZONDEK, H. AND A. TICHO. Observations on so-called thyrotropic exophthalmos. *Brit. M. J. 1:* 836 (1945).

Three cases of exophthalmos are reported which were originally classified as thyrotropic exophthalmos. The opthalmic manifestations were of a particularly severe degree in all three cases. Two presented marked decalcification of the skull bones and enlargement of the sella turcica pointing to involvement of the pituitary-diencephalic region. These cases had diabetic, glucose tolerance curves. An abnormally high blood cholesterol level was present in two cases. The basal metabolic rates were +15, +19, +60 per cent. All three cases responded favorably to diiodotyrosine. In one case diiodotyrosine in combination with pituitary irradiation on two occasions resulted in considerable improvement of the eyes and thus rendered surgical intervention unnecessary. In view of the fact that the part played by the thyrotropic hormone in production of this kind of exophthalmos is doubtful while that of the pituitary-diencephalic system seems to be highly probable, the looser definition of pituitary-diencephalic exophthalmos is suggested.—*L.T.S.*